THE UNIVERSITY OF ALBERTA

SYNTHETIC STUDIES RELATED TO FREDERICAMYCIN A

by

SHARON MARGARET BENNETT

A THESIS

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IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

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FALL 1986

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submitted by SHARON MARGARET BENNETT

in partial fulfilment of the requirements for the degree of DOCTOR OF PHILOSOPHY.

Supervisor

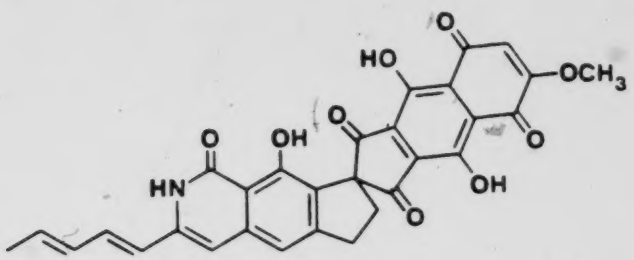
External Examiner

DATE: MAY 12, 1986

To my parents

ABSTRACT

This thesis describes the development of methodologies applicable to the synthesis of the antitumor antibiotic fredericamycin A (**1**).



Fredericamycin A **1**

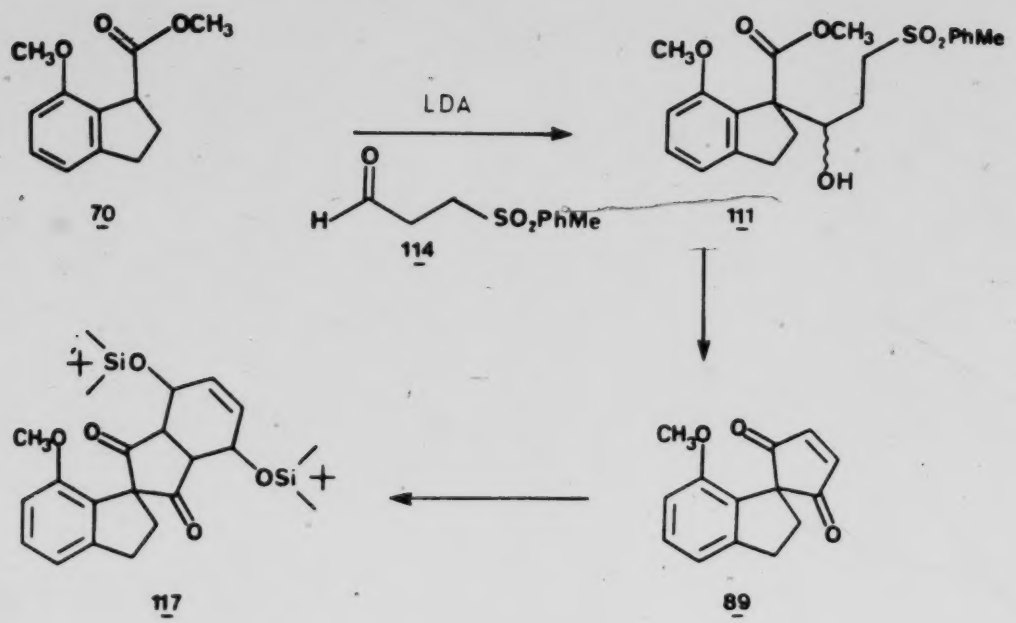
Analogues **117** and **118** were prepared by two different routes. These compounds contain the central tetracyclic spiro system of fredericamycin.

The preparation of **117** involved the use of high pressure Diels-Alder chemistry (Scheme A) and compound **118** was made by extension of a radical cyclization technique previously developed in this laboratory (Scheme B).

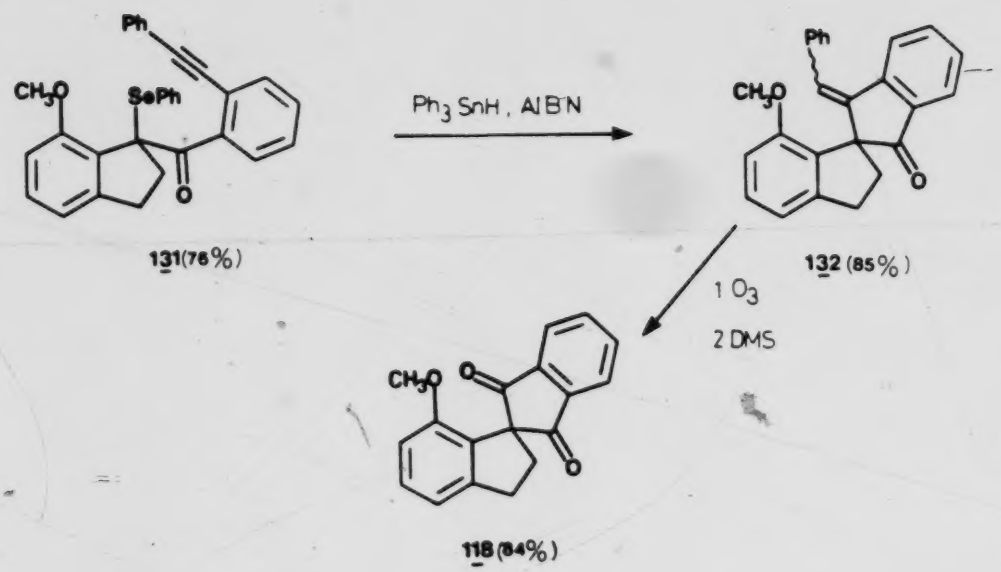
Studies on more highly functionalized analogues of **118** are also reported.

The published synthetic work towards fredericamycin has been reviewed and a summary of synthetic methods for constructing spiro systems, similar to that found in the natural product, is presented.

Scheme A



Scheme B



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My thanks extend also to the Alberta Heritage Foundation for Medical Research and to the University of Alberta for financial support.

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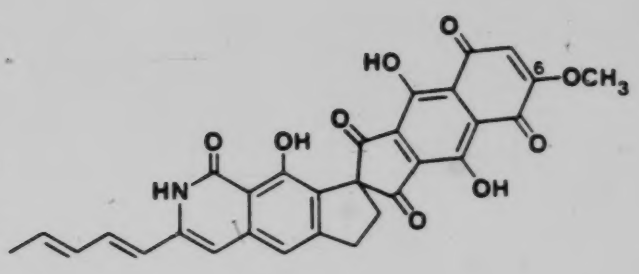
I. INTRODUCTION

Fredericamycin A (**1**) is an antitumor antibiotic produced by Streptomyces griseus (FCRC-48).[1] It is active against fungi and Gram-positive bacteria and shows an *in vitro* activity against mouse leukemias P388 and L1210 comparable to that of actinomycin D and adriamycin.[2] It also exhibits *in vitro* activity against human glioblastoma cells and *in vivo* activity against P388 and CD8F tumors.[2]

The X-ray structure of fredericamycin[3] shows it to be a hexacyclic compound composed of two perpendicular plates. This is a novel ring system, not previously found among antibiotics.[3] Biosynthetic studies have shown that the entire carbon skeleton of fredericamycin is derived from acetate.[4] The only non-skeletal carbon is that of the methoxy group at C-6 and this carbon originates from L-methionine.[4]

The mechanism of cellular action of fredericamycin is not known, although preliminary studies suggest that it interferes with protein synthesis.[2] If a number of structural analogues were available one might be able to obtain information on the structure-activity relationships of this molecule and hence gain some understanding of its mode of action. One approach to a series of analogues is



Fredericamycin A

(1)

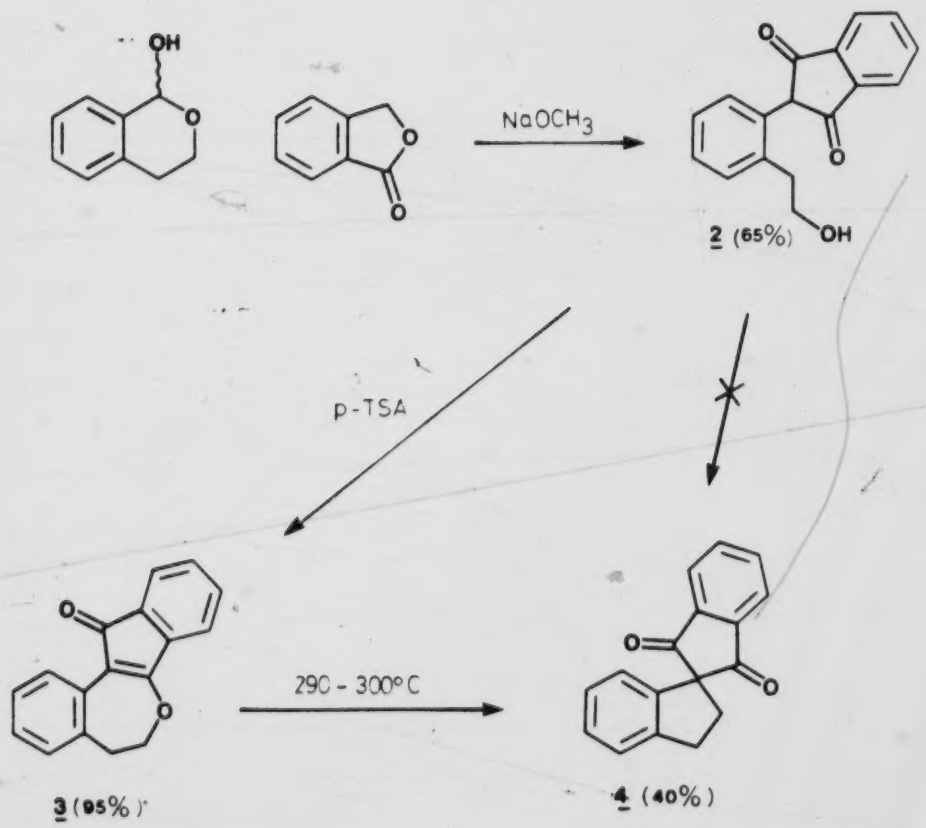
by derivatizing the natural product and this has been done by the S.S. Pharmaceutical Co., Ltd. whose scientists report antitumor activity for a number of fredericamycin derivatives.[5,6] An alternate and, more flexible route to appropriate analogues, is by chemical synthesis.

The biological activity and the novel skeleton of fredericamycin make it an interesting synthetic target and provide an opportunity to develop new routes to functionalized spiro compounds. When we began work on fredericamycin early in 1983 there were no publications on the synthesis of this molecule, but, since that time, seven reports have appeared that deal with the spirocyclic center of fredericamycin although no total synthesis has

yet been published. As a means of introducing our work, a review of the seven reported methodologies is given, followed by a summary of recent literature methods applicable to the construction of oxygenated spiro[4,4]nonane systems.

1. The first reported synthesis of a spiro compound related to fredericamycin involved thermal isomerization of **3** to **4** (Scheme 1) as the key step.[7] Compound **3** was

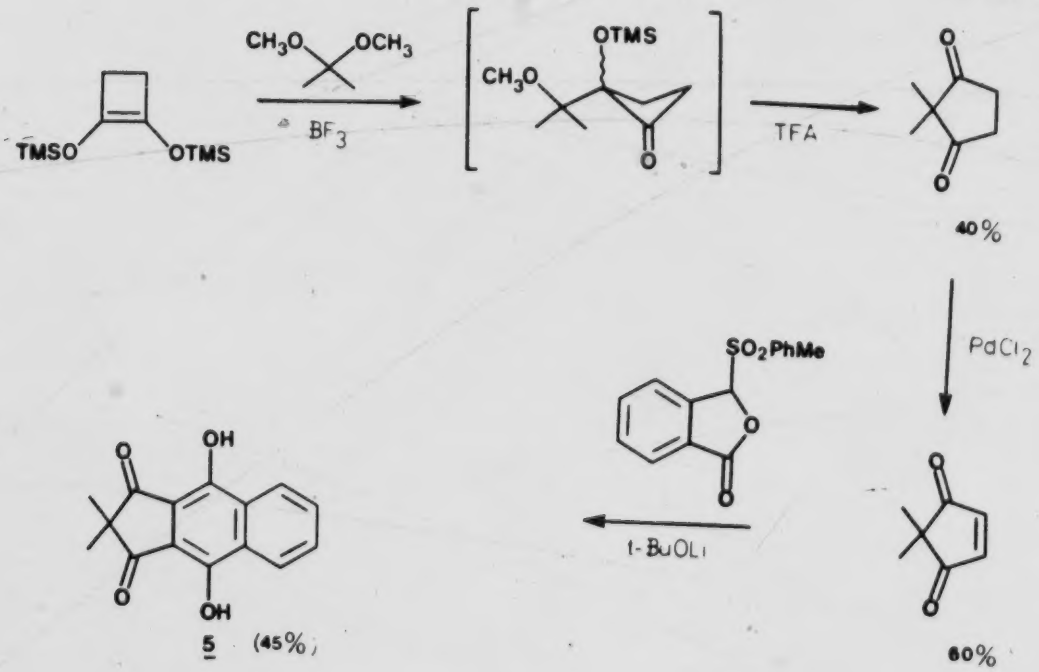
Scheme 1



prepared from phthalide and 1-hydroxyisochroman: Dieckmann condensation of these compounds gave **2** and treatment with <u>para</u>-toluenesulfonic acid then produced **3**. This was isomerized thermally to the spiro compound **4**.

2. In a model study,[8] the benzindendione **5** was prepared by a method that should be applicable to spiro compounds. The approach (Scheme 2) is based on the Kuwajima aldol/ring expansion[9] and Hauser's quinone annulation methodology.[10]

<u>Scheme 2</u>

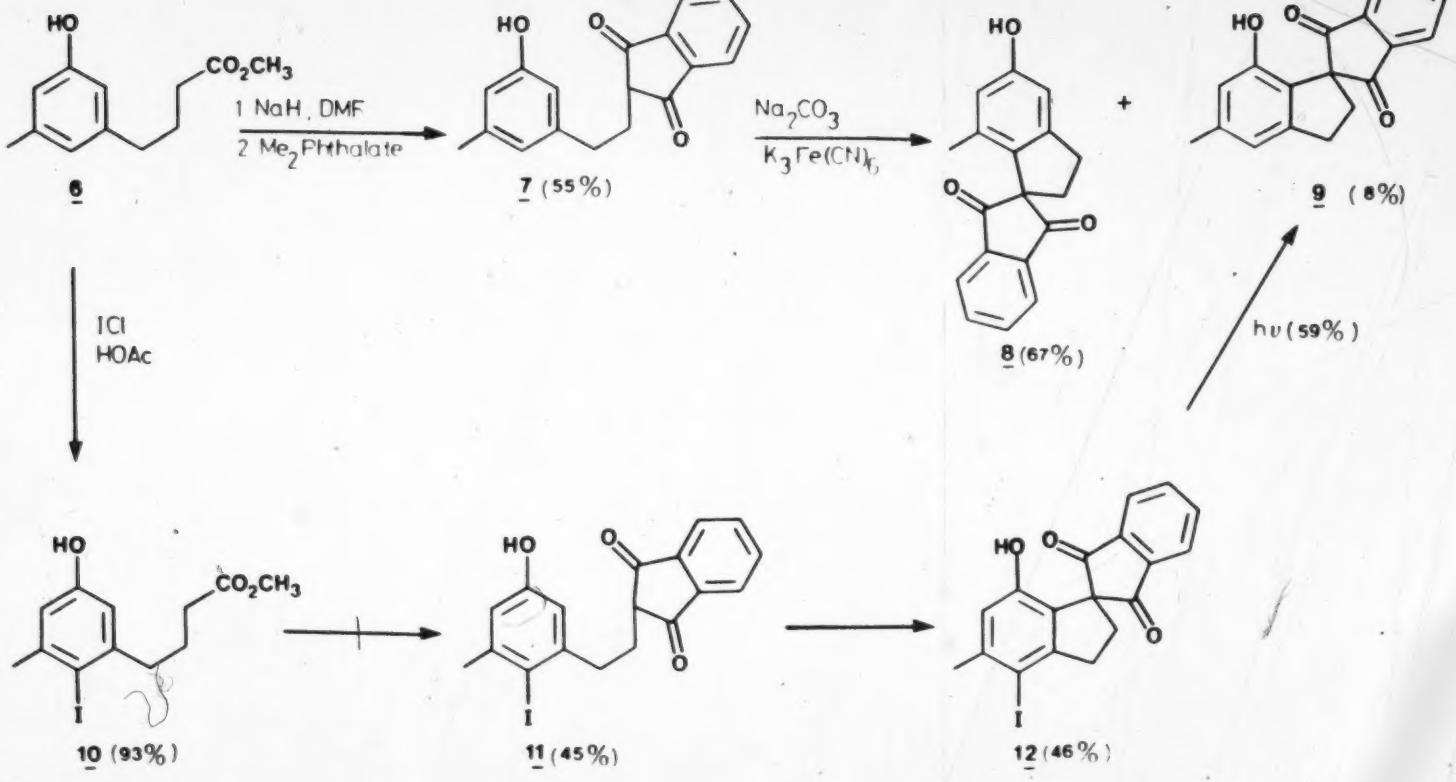


3. Phenoxy radicals have been employed[11] to make the spirocyclic center of fredericamycin (Scheme 3). The starting material, compound **6**, was prepared in a four step sequence from 3,5-dimethylphenol, and condensation of **6** with dimethyl phthalate gave substrate **7**. Exposure of **7** to potassium ferricyanide under mild alkaline conditions produced a mixture of the para-coupled product **8** (67%) and the desired ortho-coupled material **9** (8%). When the para-position of **7** was blocked by an iodine substituent, as in **11**, the oxidative coupling gave only the desired spiro diketone **12** (46%). Photochemical reduction of iodide **12** then gave **9** (59%) along with recovered starting material (25%).

One of the groups working on fredericamycin synthesis has reported the preparation of spirohydrindandione systems by Friedel-Crafts reactions[12] and by means of spiroalkylation and oxidation.[13]

4. Their first method,[12] summarized in Scheme 4, involved condensation of 1,4-dimethoxybenzene **13** with 1,1-cyclopentanedicarboxylic acid or 1,1-indandicarboxylic acid to generate spiro compounds **14** and **15**, respectively.

5. Their second method,[13] outlined in Scheme 5, involved spiroalkylation of indene **16** with bis-1,2-(bromomethyl)benzene or 2,3-bis(bromomethyl)-1,4-dimethoxybenzene. The spiro products **17** (no yield reported) and

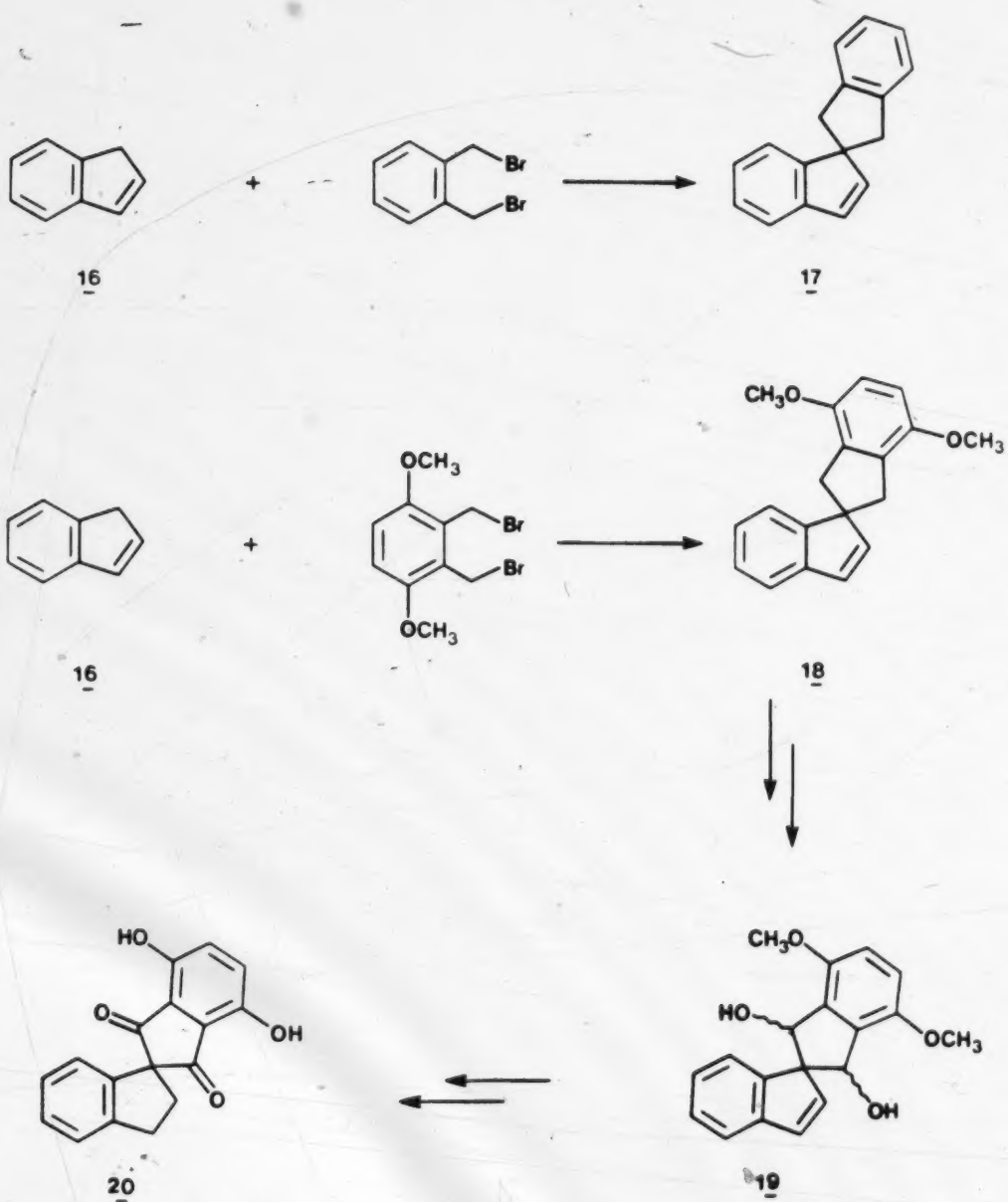

HO
CO2CH3
1 NaH, DMF
2 Me2 Phthalate
6
7 (55%)
Na2CO3
K3Fe(CN)6
8 (67%)
9 (8%)
hυ (59%)
ICl
HOAc
10 (93%)
11 (45%)
12 (46%)
I
O

Scheme 3

Scheme 4

CH3O
CH3O
O
O
14 (50%)
MeSO3H - P2O5
CH3O
CH3O
13
+
CO2H
CO2H
OCH3
CH3O
O
O
15 (10%)
MeSO3H - P2O5
CH3O
CH3O
13
+
CO2H
CO2H

Scheme 5

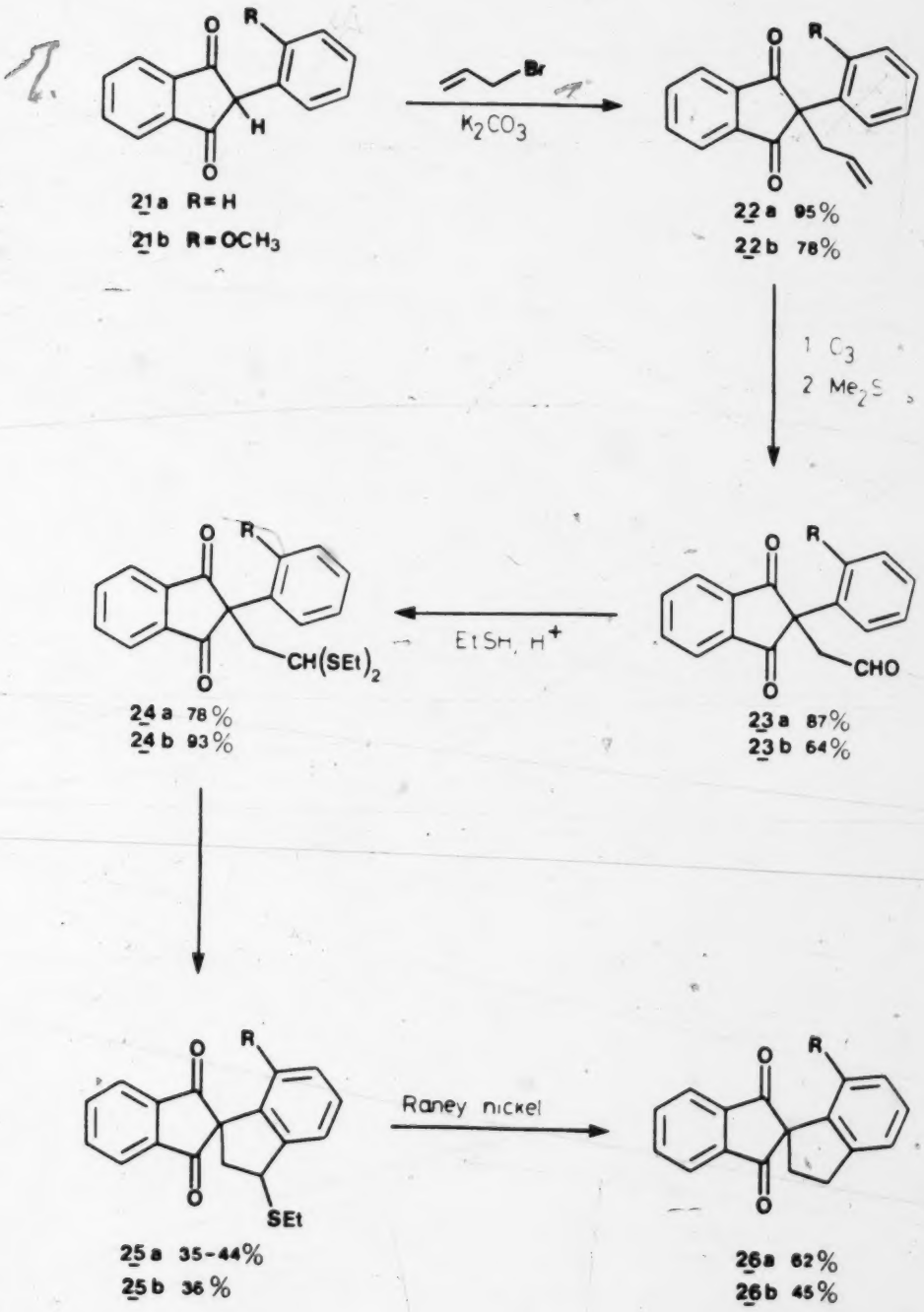

Br
Br
16
17
OCH3
Br
Br
OCH3
CH3O
OCH3
16
18
HO
O
OH
O
20
CH3O
HO
OCH3
OH
19

18 (34%) were obtained. Conversion of **18** to the dione **20** was accomplished in a six step sequence: benzylic bromination, displacement of bromide with acetate and subsequent treatment with lithium aluminum hydride gave the diol **19**. Catalytic hydrogenation of the double bond, followed by oxidation and removal of the O-methyl protecting groups led to the spiro[4,4]nonane system **20** in 12.6% overall yield from **18**.

6. A method based on intramolecular Friedel-Crafts reaction is outlined in Scheme 6.[14] When attempts to convert aldehyde **23a**, readily prepared from **21a**, into a spirocyclic alcohol were unsuccessful, the derived thioacetals **24a** (78%) and **24b** (93%) were prepared. These were cyclized by treatment with silver perchlorate, silver tetrafluoroborate, or aluminum trichloride to give **25a** (35-44%) and **25b** (36%). Desulfurization of the products gave the spiro compounds **26a** (62%) and **26b** (45%).

7. The final method[15] that has been reported to date is outlined in Scheme 7 and has some similarity with method 2. Lewis acid catalyzed aldol reaction of the bicyclo-bis[trimethyl(siloxy)]butene **27** with dithioacetal **28** gave compound **29** as a mixture of diastereoisomers (84%). A stereospecific mercury catalyzed rearrangement of **29** gave **30** (81%). Bromination and elimination of

Scheme 6



21a R=H
21b R=OCH_3

22a 95%
22b 78%

23a 87%
23b 64%

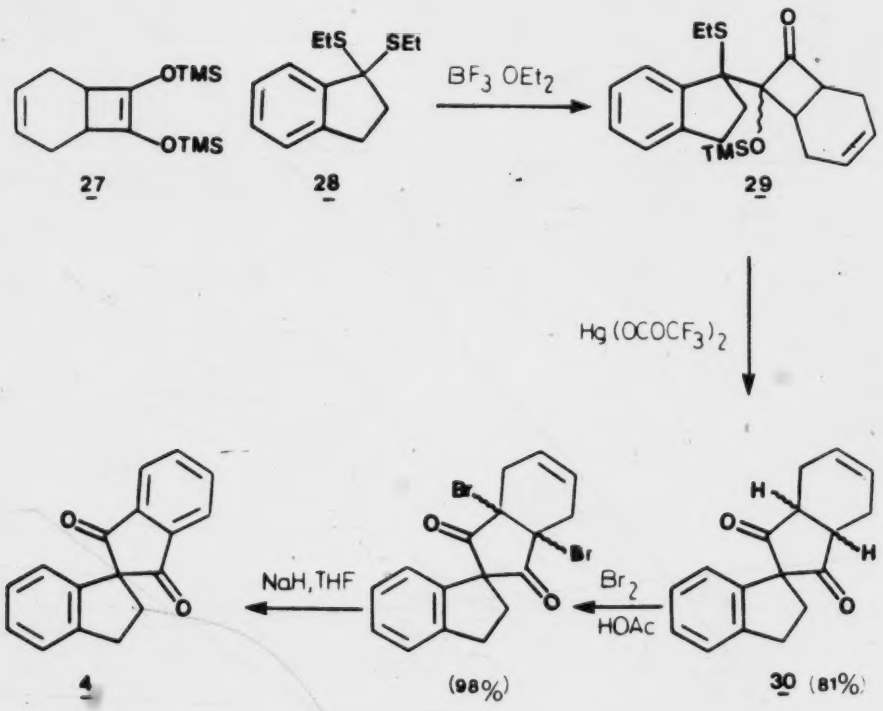
24a 78%
24b 93%

25a 35-44%
25b 36%

26a 62%
26b 45%

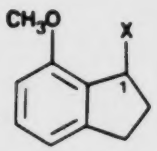
hydrogen bromide gave the spiro[4,4]nonane **4**.

Scheme 7



In our own work we chose to use a methoxyindane of the general type **31** as our starting material for synthesis of spiro compounds related to fredericamycin. Compound **31** contains two of the rings of the hexacyclic skeleton of

the natural product and we planned to attach the spiro unit at the C-1 position.

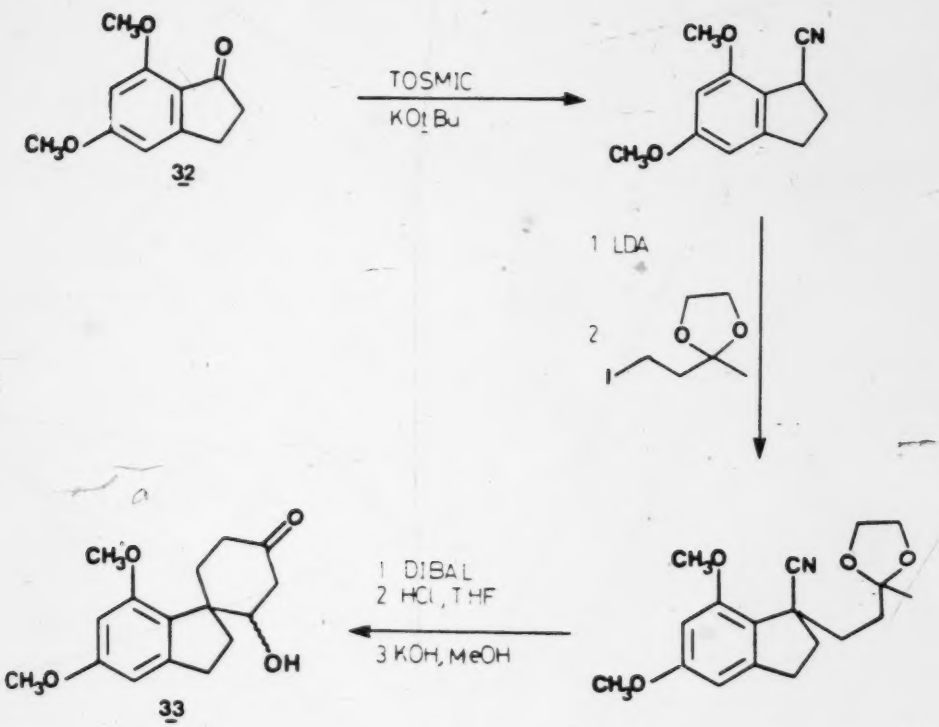


31

The general topic of synthesis of carbocyclic spiro compounds has been extensively reviewed.[16-23] Examples of methodologies which have been used specifically for synthesis of spiroindanes are listed below so as to provide some background information on our proposed strategy. Much of the work on spiroindanes has been published in the patent literature and details of some of the transformations are not reported in the Chemical Abstracts we examined. Examples of recently published methods (not yet reviewed) for constructing functionalized spirocyclopentanes have also been included.

The synthetic strategy[24,25] used for making the cannabis spirans is outlined in Scheme 8. One carbon homologation of dimethoxyindane **32** was followed by alkylation or Michael addition to attach an appropriate side chain, and after functional group manipulations, an aldol reaction was used to generate the [4,5] spiro systems of type **33**.

Scheme 8

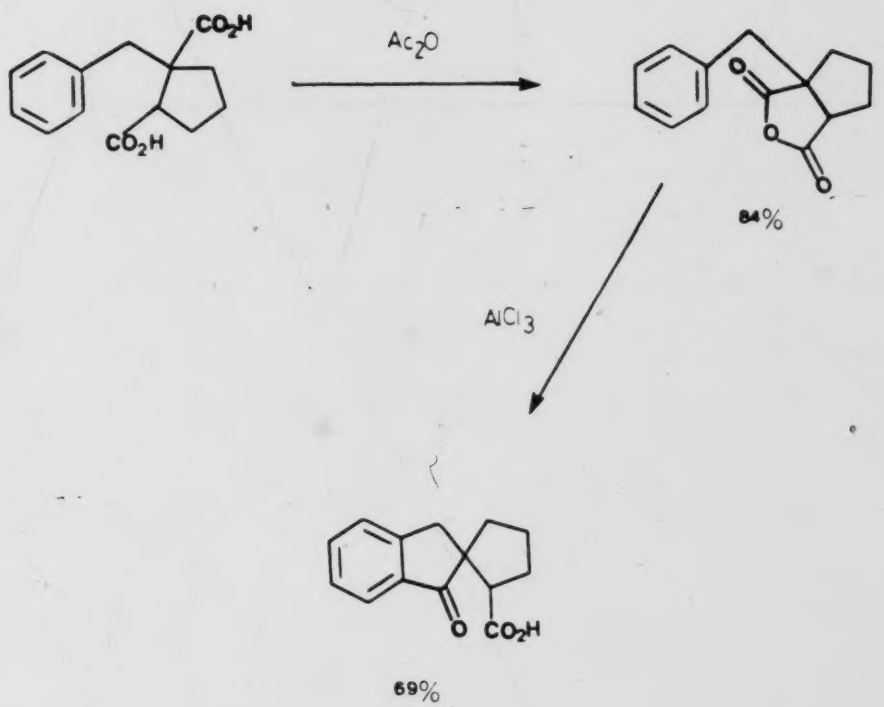


Friedel-Crafts acylation has been employed extensively in the preparation of spiroindane compounds and two examples are shown in Schemes 9[26] and 10[27].

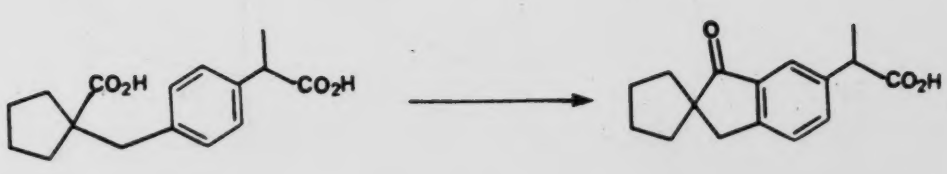
Dialkylation of indanone **34** (Scheme 11) with 1,5-dibromopentane gave spiro compound **35**.[28]

Diacylation of the heterocyclic compound **36** (Scheme 12) with phthalic anhydride produced spiro[4,4]nonane system[29] **37**.

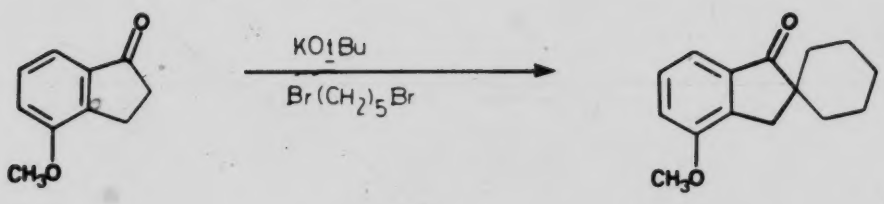
Scheme 9



Scheme 10

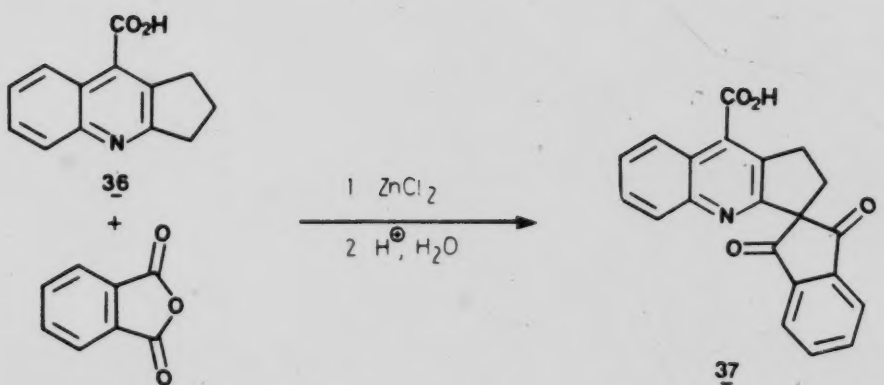


Scheme 11



34 35

Scheme 12

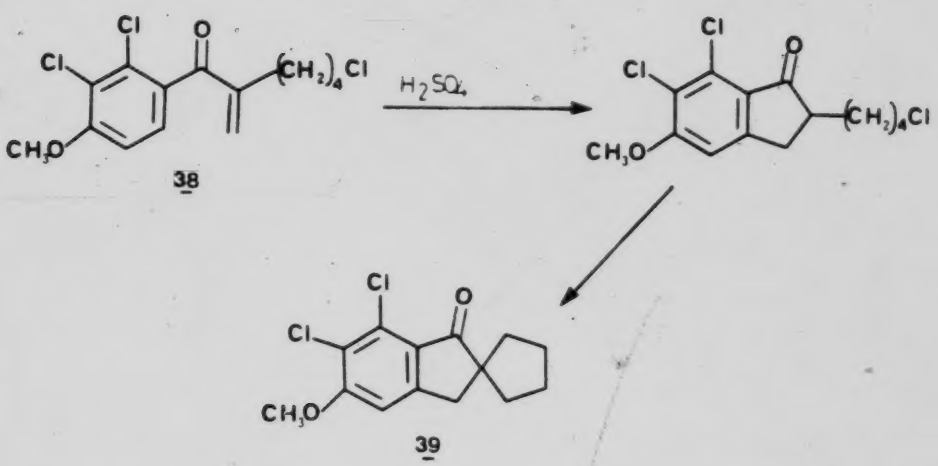


36 37

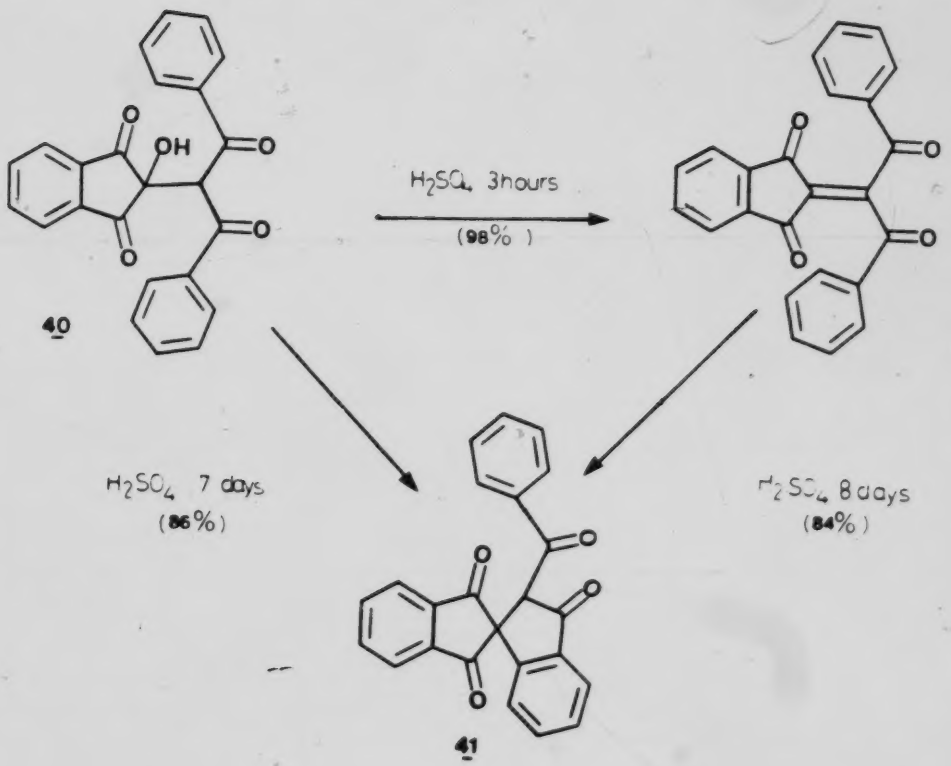
Acid catalyzed ring closure of compounds of type **38** (Scheme 13) and subsequent spiroalkylation affords spiroindanone **39**.[30]

Dehydration of indandione **40** (Scheme 14) followed by acid catalyzed ring closure afforded the spiro compound **41**

Scheme 13



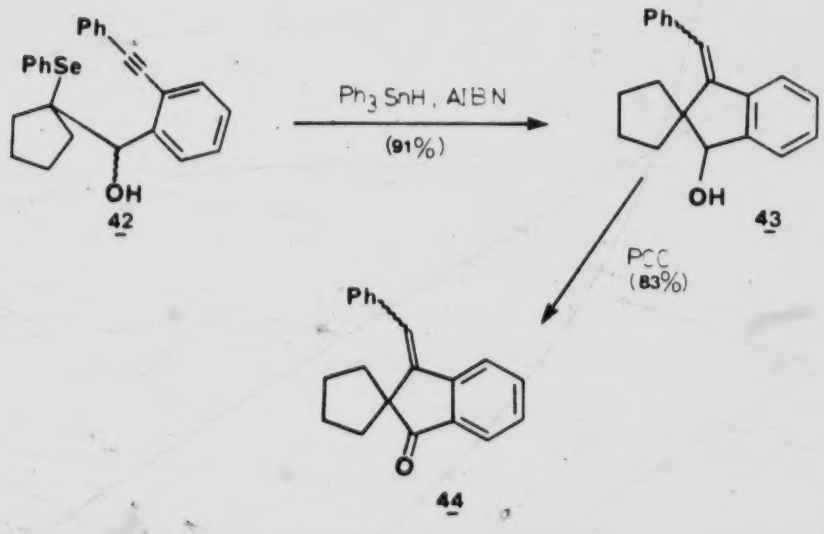
Scheme 14



in high yield.[31]

Radical cyclization methodology has recently been applied in this laboratory to synthesis of spiroindanes.[32] Homolytic cleavage of the carbon-selenium bond of compounds of type **42** (Scheme 15) led to indane **43** and oxidation then provided the [4,4]spiroindanone **44**.

Scheme 15

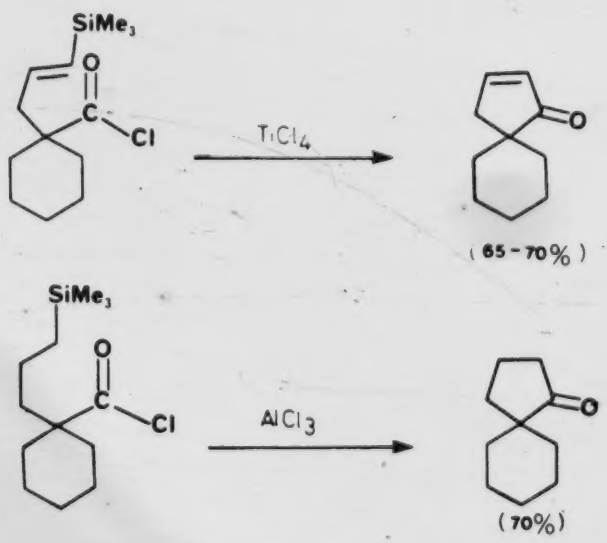


Thermal rearrangement of enol silyl ethers of 2-(cyclopropylmethylene)cycloalkynones was used to carry out five membered ring spiro annulations.[33] For example, rearrangement of **45** (Scheme 16) and hydrolysis provided the spiro[4,4]nonane **46**.

Scheme 16

Lewis acid mediated intramolecular acylation of vinyl silanes[34] and alkyl silanes[35] provides a route to spirocyclopentenones and spirocyclopentanones respectively, as outlined in Scheme 17.

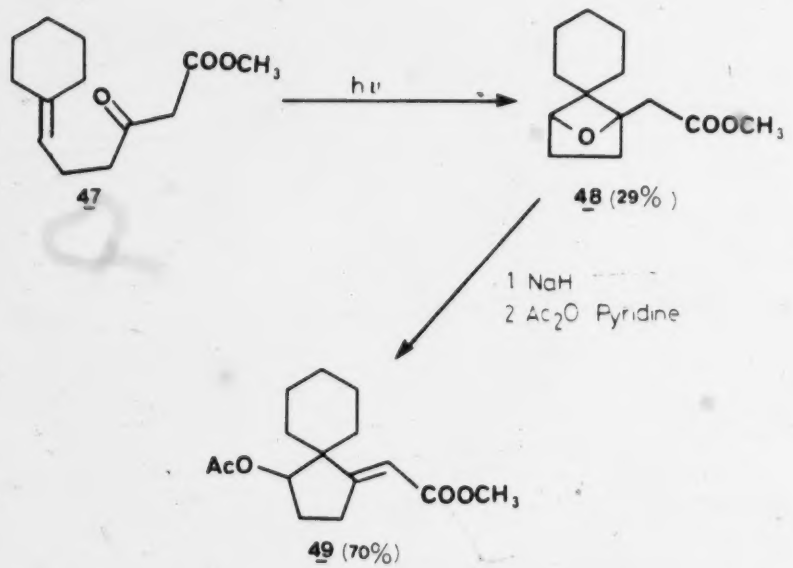
Scheme 17



Photocycloadditions have also been used as the key step in the synthesis of several spiro[4,5]systems.

Photolysis of **47** to give oxetane **48** was the key step in formation of spiro[4,5]decanol **49** (Scheme 18).[36]

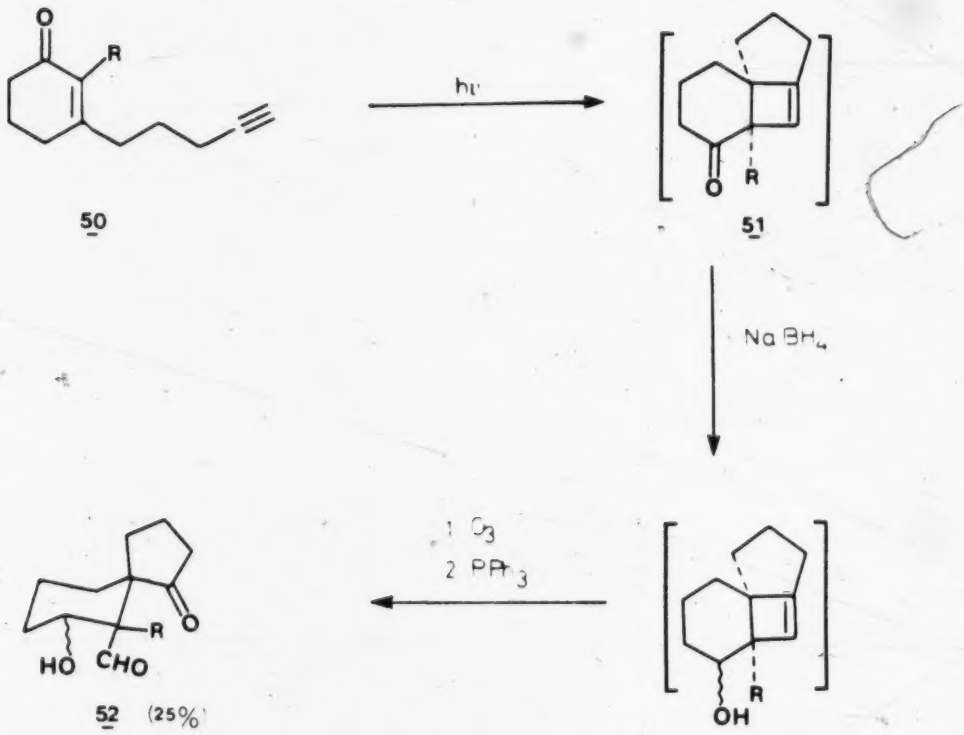
Scheme 18



An intramolecular [2+2]cycloaddition[37] was used to prepare compound **51** from **50** (Scheme 19). Sodium borohydride reduction and ozonolysis afforded the spirodecanone **52** in 25% overall yield from **50**.

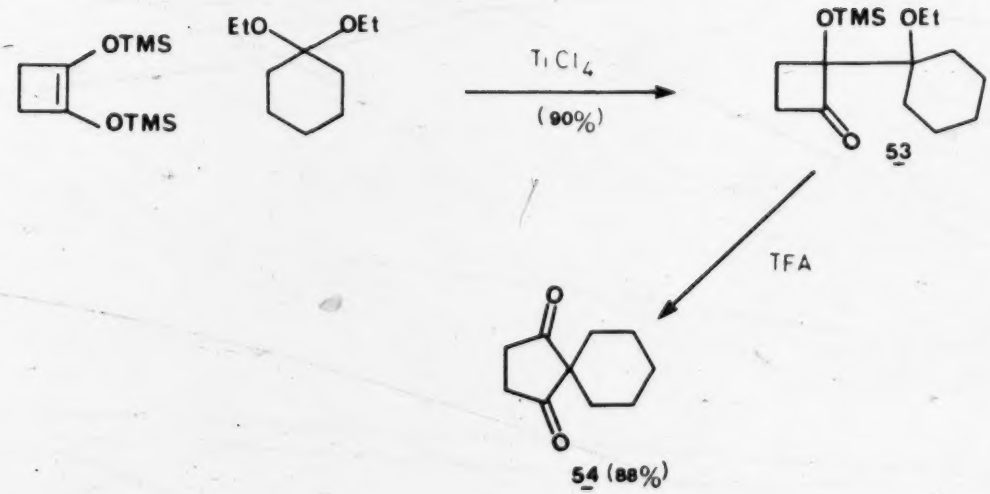
One spiroannulation method[38] which has already been used to prepare fredericamycin analogues is the two step procedure (Scheme 20) that involves Lewis acid catalyzed aldol reaction of bis(trimethylsilyloxy)cyclobutene and an acetal to give a succinoin derivative. The acid catalyzed

Scheme 19



50 51 52 (25%)

Scheme 20



53 54 (88%)

rearrangement of compounds of type **53** led to the spirocyclopentadione **54**.

As has been mentioned, we decided to use a methoxyindane of type **31** as the starting material for our synthesis of molecules related to fredericamycin. The group X must satisfy certain requirements: it should permit acylation (or alkylation) at C-1 and it should facilitate construction of the spirocyclopentadione ring, possibly by incorporation into that unit or by acting as a precursor to a reactive intermediate that can undergo spirocyclization.

In the following section four topics are discussed:

A. Synthesis of functionalized dihydroindenes of type **31**.

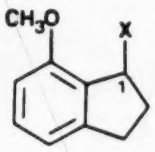
B. Attempted synthesis of spiro compounds by use of diacylation or Friedel-Crafts reactions.

C. Synthesis of spiro compounds by acylation and Diels-Alder chemistry.

D. Synthesis of spiro compounds by radical cyclization.

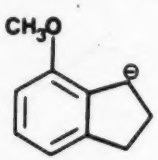
II. RESULTS AND DISCUSSION

A. Synthesis of Functionalized Dihydroindenes

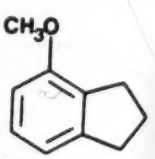


31

As discussed in the previous section we planned to start with a methoxyindane of type **31**. The simplest choice of X is hydrogen because a heteroatom-directed lithiation at the benzylic position *peri* to the methoxy group would generate the desired carbanion **55**. Precedent for this process exists in the reported preparation of 2-methoxyphenylacetic acid from 2-methoxytoluene by reaction with *n*-butyllithium (followed by carbon dioxide).[39] Our starting material, 4-methoxyindane **56**, was prepared by methylation of commercially available 4-indanol.



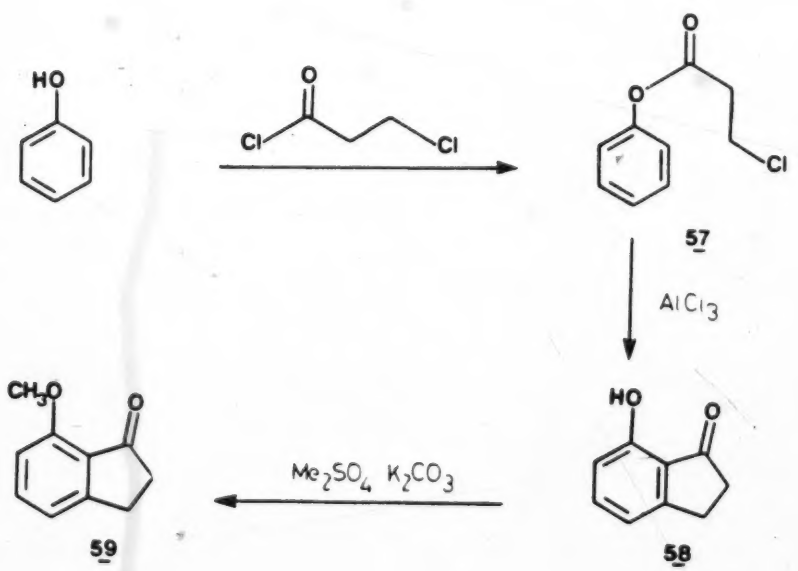
55



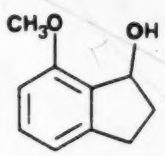
56

Treatment of **56** with n-butyllithium or t-butyllithium in cyclohexane failed to produce the required carbanion in any detectable amount. We decided, therefore, to introduce the substituent X (see **31**) by the following route: 7-hydroxyindanone **58** was prepared in large quantities from phenol and 3-chloropropionyl chloride by a published method.[40] The hydroxyl group was protected as its methyl ether so as to give 2,3-dihydro-7-methoxyinden-1-one **59**, which served as the starting material for preparation of several compounds of general type **31**.

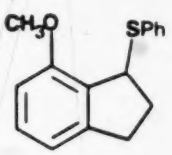
Scheme 21



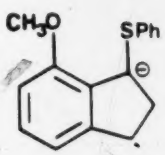
Sodium borohydride reduction of ketone **59** gave the indanol **60**; however, attempts to cleanly convert **60** to the corresponding bromide,[41] nitrile,[42] or mesylate[43] were unsuccessful. Each of these transformations was complicated by partial or complete elimination of water. However, it was possible to convert alcohol **60** into sulfide **61**, in moderate yield (56%) by use of diphenyldisulfide and tributylphosphine.[44]



60



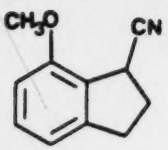
61



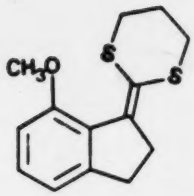
62

Sulfide **61** was successfully deprotonated with sec-butyllithium (THF, 3 h, -78°C) but attempts to acylate the resultant carbanion **62** with simple electrophiles such as benzaldehyde or benzoyl chloride were unsuccessful.

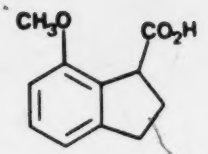
We next considered use of one carbon homologues of ketone **59** such as nitrile **63**, ketenethioacetal **64**, and carboxylic acid **65**.



63



64

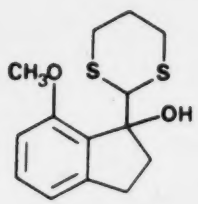


65

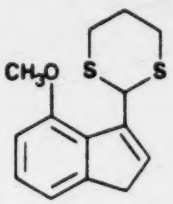
(p-Toluenesulfonyl)methyl isocyanide has been used[24] to convert 5,7-dimethoxyindan-1-one directly to the corresponding dimethoxyindan-1-carbonitrile (84%) but attempts to carry out this same transformation with our indanone **59** under a variety of reaction conditions[24,45,46] were unsuccessful. The reactions were monitored by thin layer chromatography (TLC), and infrared (IR) and/or ^{1}H nuclear magnetic resonance (NMR) (80 MHz) spectra were run on the crude and chromatographed products. We observed that either the starting materials failed to react or they both decomposed.

We next tried to prepare ketenethioacetal **64**[47,48] with the intent of hydrolyzing it to a carboxylic acid, but attempts to do this by condensation of 2-lithio-2-trimethylsilyl-1,3-dithiane with ketone **59** were unsuccessful. We could condense **59** with the simpler anion, 2-lithio-1,3-dithane[49] to produce alcohol **66** (42%); however, dehydration with p-toluenesulfonic acid, or

pyridine and thionyl chloride, both gave the endocyclic olefin **67** and not the desired exocyclic isomer **64**.



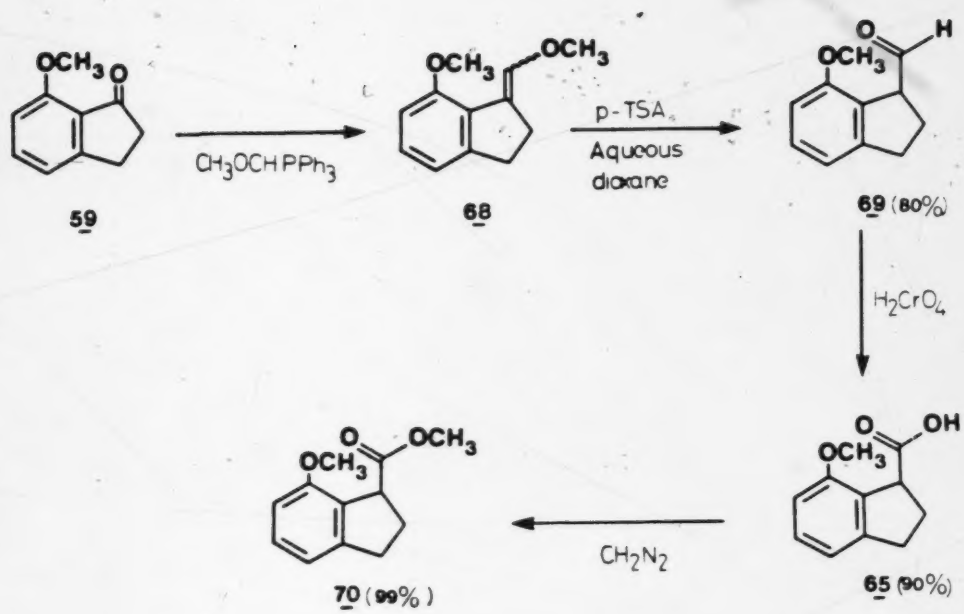
66



67

Hydrolysis of dithioacetal **67** with mercury(II) chloride[50] or thallium(III) nitrate trihydrate,[51] to the corresponding α,β-unsaturated aldehyde could not be accomplished. TLC analysis of the reaction mixtures showed the presence of several compounds, and the IR spectra of the total reaction products showed no significant carbonyl absorption. We tried to reduce the double bond of dithioacetal **67** by hydrogenation, using either palladium on charcoal or tris(triphenylphosphine)rhodium(I) chloride as catalysts. Diborane reduction was also examined. In all three cases only starting material was recovered.

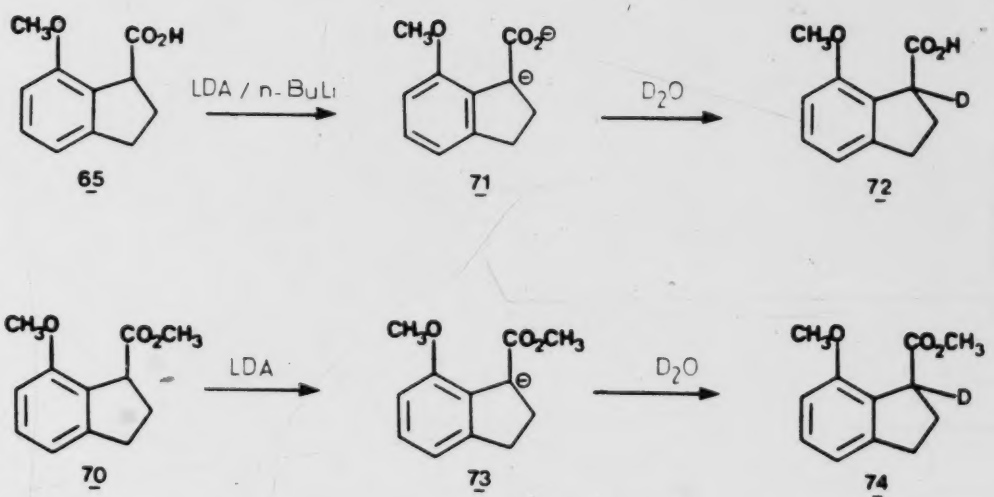
Scheme 22



Finally, homologation of methoxyindanone **59** was achieved by Wittig reaction with (methoxymethylene)triphenylphosphorane, using a modified procedure reported[52] for the corresponding 5,7-dimethoxyindanone. The resulting enol ether **68** was partially purified and hydrolyzed in refluxing aqueous dioxane to give aldehyde **69** (80% overall yield). Careful oxidation with Jones reagent[53] afforded carboxylic acid **65**. We found that the chromic acid must be added slowly to a cold (0°C) solution of the aldehyde in acetone and that it is essential to work up the reaction as soon as all the starting material

has reacted. When these precautions are not taken one isolates 7-methoxyindanone **59** along with the desired acid **65**. Esterification of **65** with diazomethane or dimethyl sulfate and potassium carbonate provided methyl ester **70**.

Scheme 23



The dianion **71** was prepared from acid **65** and either LDA[54] [2.2 equivalents in THF, -78°C (1 h), 50°C (1 h)] or n-butyllithium[55] [2.1 equivalents in THF, 0°C, 1 h], and quenched by addition of deuterium oxide. The percentage of deuterium at C-1, as determined by ^{1}H NMR, was used to assess the efficiency of carbanion formation. Likewise,

the α-carbanion of ester **70** was efficiently prepared by addition of **70** to LDA (1.5 equivalents in THF, -78°C, 1 h).

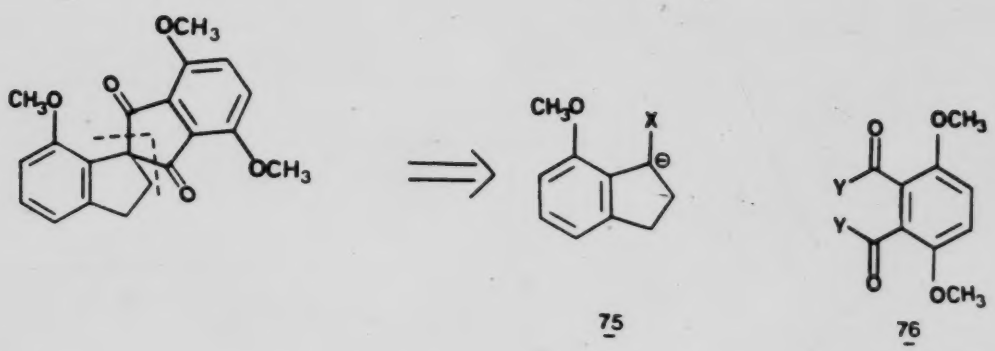
This route, based on Wittig methodology for one-carbon homologation of indanone **59**, provided us with three compounds (**69**, **65**, **70**) which fit our general requirements (see **31**), although in practice we have studied the acylation and alkylation only of the acid **65** and its methyl ester **70**.

B. Attempted Synthesis of Spiro Compounds by Use of Diacylation or Friedel-Crafts Reaction

We examined several ways of constructing the central four rings of fredericamycin. One retrosynthetic analysis (Scheme 24) involved dissection of the molecule to give the two synthons **75** and **76**, where we envisaged both carbonyls of the spiro[4,4]nonane system to originate from an electrophile such as an anhydride. To test this approach, we tried to acylate the α-carbanion of methyl ester **70** with phthalic anhydride. Analysis [TLC, ^{1}H NMR (200 MHz)] of the reaction products showed a complex mixture of polar compounds which were not separable by chromatography.

Diethyl 3,6-dimethoxy-1,2-dicarboxybenzene **79** was

Scheme 24

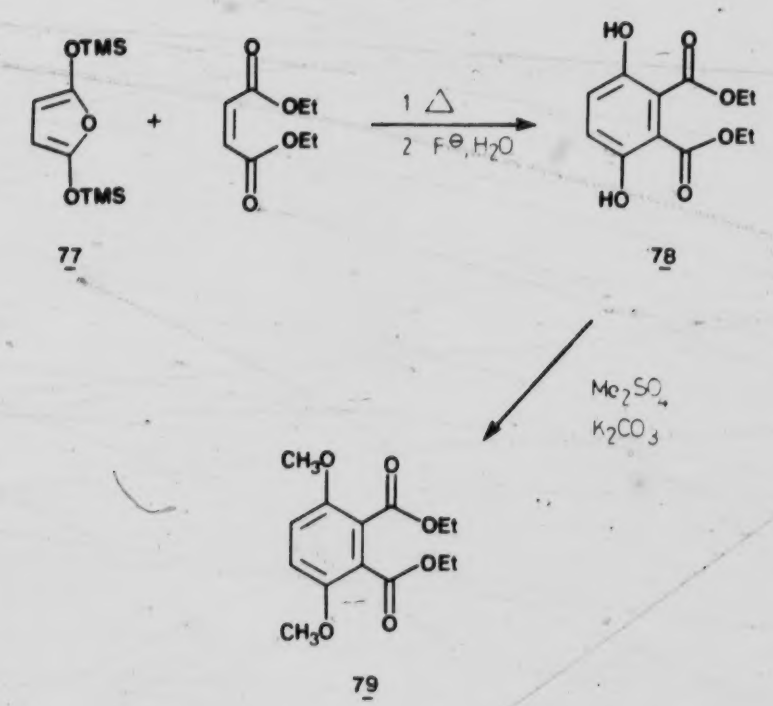


75 76

also used as an electrophile to evaluate this diacylation approach. The preparation of diester **79** is outlined in Scheme 25. Diels-Alder reaction of the 2,5-bis(trimethylsiloxy)furan[56] **77** and diethyl maleate followed by aqueous work-up with fluoride ion gave diethyl 3,6-dihydroxy-1,2-dicarboxybenzene **78**. The hydroxyl groups were then protected by methylation to give **79**. The attempted acylation of dianion **71** with diester **79** was unsuccessful. The only major reaction components that could be isolated were the unreacted starting materials.

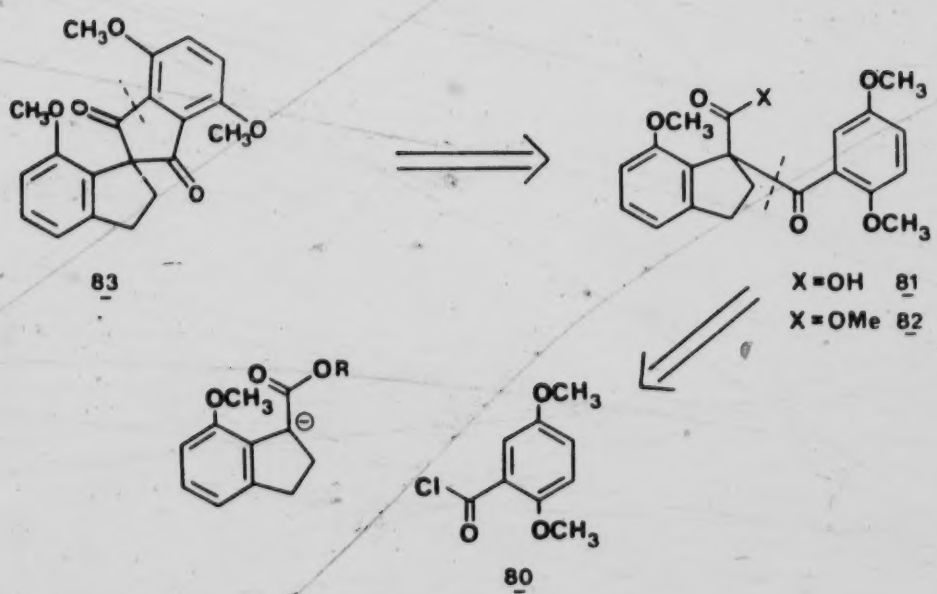
A second route, that also proved unsuccessful, involved a Friedel-Crafts acylation approach to the spiro system. In this case we envisaged the key step as a ring closure to form the fused spirocyclopentandione (Scheme 26).

Scheme 25



77 78 79

Scheme 26

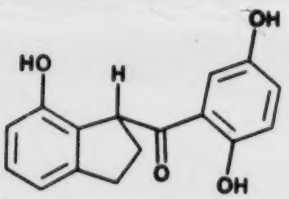


83 80

The usual reactive functional groups for Friedel-Crafts acylations are acid chlorides or acids. With our system **81** [X = OH] there is the added complication of decarboxylation of the β-ketoacid, and so we chose to study ring closure of β-ketoester **82**. Esters are not commonly used in Friedel-Crafts acylations but we hoped that the two methoxy substituents would sufficiently activate the aromatic ring and thus compensate for the less reactive nature of the ester function.

2,5-Dimethoxybenzoyl chloride **80** was prepared from the corresponding commercially available acid and condensed with carbanion **73** to give β-ketoester **82** in good yield (81%). Compound **82** failed to react upon exposure to titanium tetrachloride or aluminum chloride at room temperature. It was equally inert to boron trifluoride etherate at room temperature or 100°C. When β-ketoester **82** was treated with p-toluenesulfonic acid in refluxing benzene several compounds were obtained. The IR spectrum of each of the major components was inconsistent with our expectations for the cyclized product. Exposure of the β-ketoester to aluminum trichloride in refluxing benzene resulted in extensive deprotection and decarboxylation to give ketone **84**.

We decided not to pursue ring closure of compounds of type **82** and, instead, looked to a β-alkoxyacid chloride

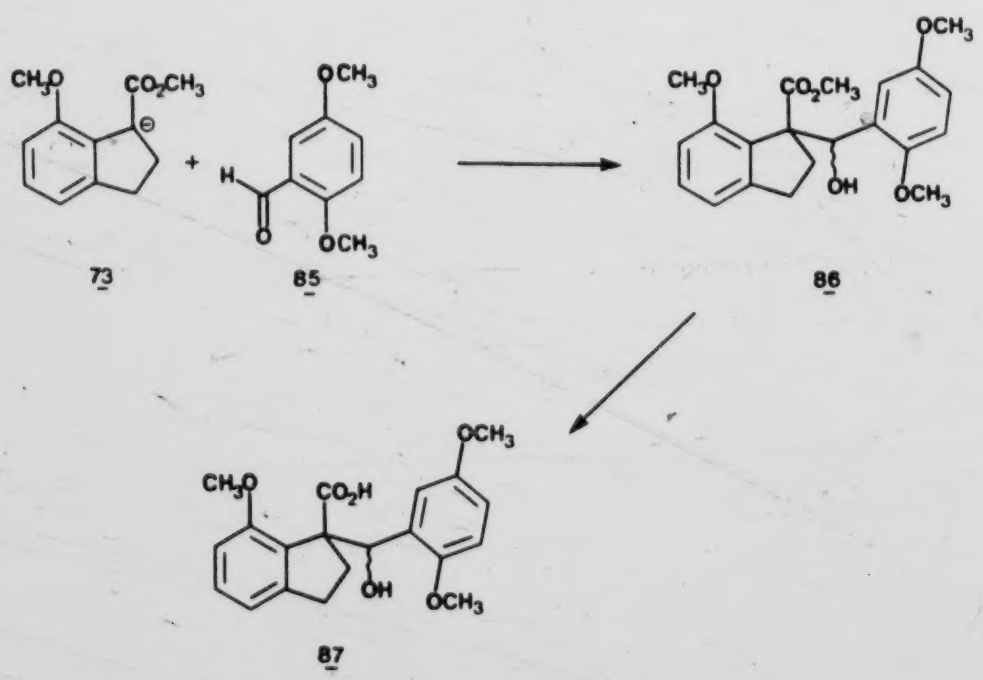


84

as an alternative starting material for a Friedel-Crafts acylation approach.

2,5-Dimethoxybenzaldehyde **85** was prepared, by oxidation of the commercially available alcohol, and condensed with carbanion **73** to give β-hydroxyester **86** (73%) as a mixture of diastereoisomers (Scheme 27).

Scheme 27



73 85 86 87

Manipulation of this compound proved to be difficult. The ester was hydrolyzed to the β-hydroxyacid **87** in low yield(25%), and an attempt to protect the β-hydroxy group of **86** as a methyl ether resulted in a retroaldol reaction to form aldehyde **85** and ester **70**. At this point we abandoned the Friedel-Crafts approach to the spiro ring system in favor of more promising routes which, in the event, proved successful.

C. Synthesis of Spiro Compounds by Acylation and Diels-Alder Reactions

One of the approaches we have used successfully to make spiro compounds is based on intramolecular acylation reactions of vinyl silanes and α-sulfonyl carbanions. We adopted these strategies in order to make spirocyclopentenedione **89**. Diels-Alder reaction of **89** with an appropriate diene would then provide tetracyclic compounds of type **88** (Scheme 28). We examined two routes to the tricyclic skeleton.

In the first route (Scheme 29) the dianion **71** was condensed with bromomethyl vinyl silane*[34] **90** to give **91**

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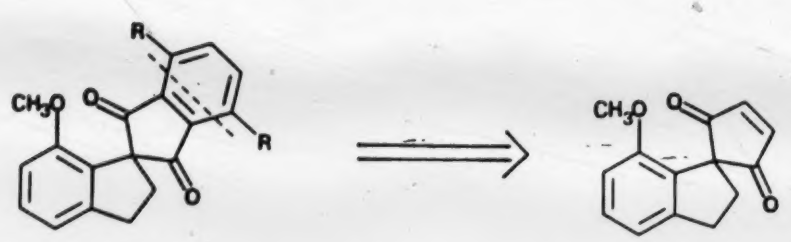
*Prepared by D.L. Lusyk from the corresponding alcohol[69] according to reference 34.

Scheme 28

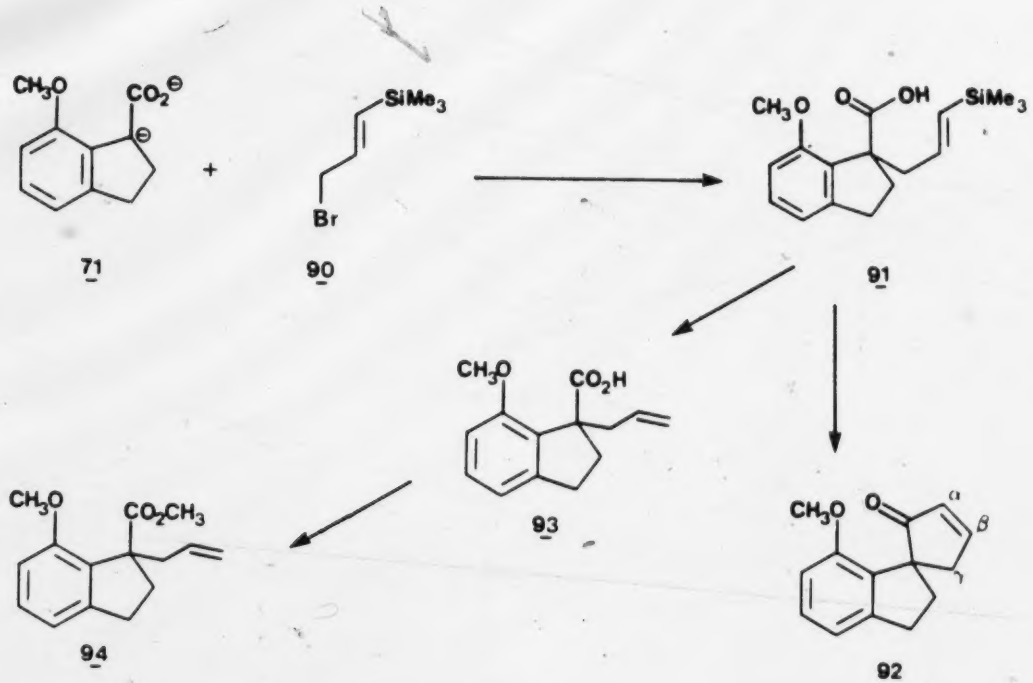


88 89

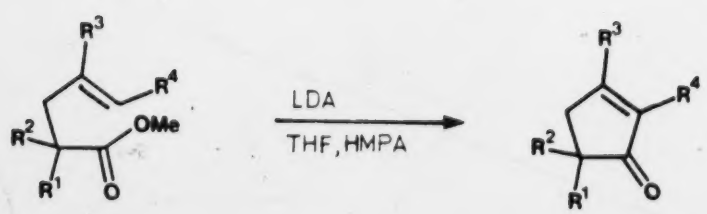
(71%). Conversion of **91** into the corresponding acid chloride and subsequent treatment with aluminum chloride[35,57] gave spirocyclopentenone **92** (66%). Although a number of other Lewis acids were tried (titanium tetrachloride,[34] ethylaluminum dichloride,[58] tin tetrachloride[34] and silver boron tetrafluoride[59]) the best results were obtained with aluminum chloride. If we simply exposed acid **91**, instead of its chloride, to aluminum chloride, we observed desilylation of the vinyl silane substituent to give **93** (80%). Although this was not the result we had hoped for, it did provide us with an opportunity to study another cyclization method (Scheme 30).

It is known that compounds of type **95** (Scheme 30) cyclize on treatment with base.[60,61] Therefore our

Scheme 29



Scheme 30

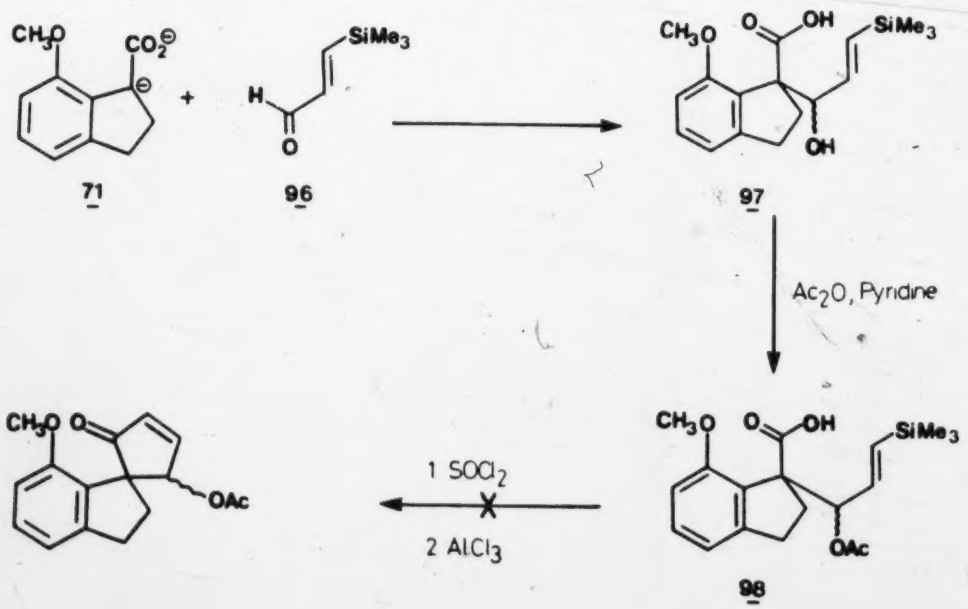


95

desilylated acid **93** was esterified and the methyl ester **94** was treated with LDA according to the literature procedure.[61] However, even after a prolonged reaction time (17 hours at room temperature) the only major component that could be isolated was the starting material.

Tricyclic compound **92**, while possessing the desired carbon framework, lacks a carbonyl at the γ position. We looked at several ways of introducing an oxygen functionality here. One possibility is to use aldehyde **96**, rather than bromide **90** as the electrophile in the initial acylation reaction (Scheme 31).

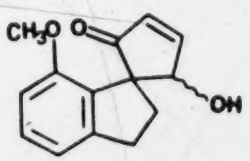
Scheme 31



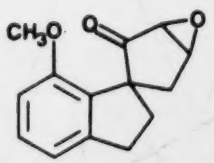
β-Hydroxyacid **97** was prepared (25%) from dianion **71** and aldehyde **96** and converted to β-acetoxyacid **98** (78%). When compound **98** was subjected to the usual reaction conditions (thionyl chloride; aluminum trichloride) no significant amount of the desired cyclized product was obtained.

Another way of incorporating a second oxygen in the cyclopentenone ring of **92** is to oxidize specifically at the γ position and one of the classical reagents for this purpose is selenium dioxide. Exposure of **92** to this reagent gave the γ-hydroxy compound **99** but the yield was very low (14%).

The use of sodium peroxide and water in ethanol to oxidize a methylene, γ to an α,β-unsaturated ketone has been reported,[62] but when we tried this reaction with **92** we obtained only the epoxide **100** (35%).



99



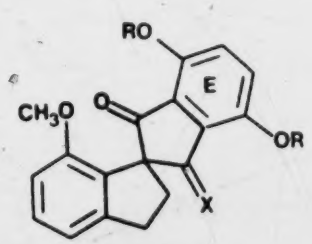
100

The method of enolate hydroxylation with a reagent such as MoOPH[63] offers another way of introducing appropriate oxygen functionality. This procedure involves

addition of the ketone to a slight excess of LDA and subsequent addition of crystalline MoOPH.[63]

The deprotonation of a spirocyclopentenone (with LDA) and subsequent reaction of the carbanion with electrophiles at the γ position of the cyclopentenone has been reported[64] and so we tested this possibility with our system. Compound **92** was treated[64] with LDA and the reaction mixture was quenched with deuterium oxide. Analysis of the crude product [TLC, ^{1}H NMR (400 MHz)] showed the presence of at least three components with the major one being the non-deuterated starting material **92**. Consequently we decided not to pursue this route.

Eventually we wanted to attach a fourth ring to the tricyclic spiro system to give compound **102**. The γ

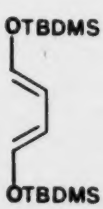


X=H$_2$ **101**
X=O **102**

position of the cyclopentenone ring in **101** has the additional advantages of being both benzylic and close to

a heteroatom substituent on ring E. We felt that if we could prepare **101**, then oxidation to **102** may prove to be more successful than our attempts to oxidize the simpler compound **92**. With this in mind, we tried a series of Diels-Alder reactions of spirocyclopentenone **92** and commercially available 1,4-diacetoxybutadiene **103** with and without Lewis acid catalysis.[65,66] None of these experiments were successful and only unreacted starting materials were recovered. Compound **92** also failed to react with (E,E)-1,4-bis[(tert-butyl(dimethylsilyl)oxy]buta-1,3-diene **104**.*,[67]

103

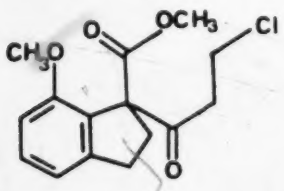


104

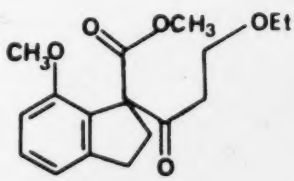
At this point we decided to stop work on cyclopentenone **92** in favor of a route which led directly to spirocyclopentenedione **89**. The key step in this approach is an intramolecular acylation of an α-sulfonyl

*Prepared from 1,4-diacetoxybutadiene by the procedure of reference 67.

carbanion.[68] Preliminary studies showed ester **70** could be condensed with simple three carbon electrophiles, such as 3-chloropropionyl chloride, to give appropriately substituted esters. If the ketone carbonyl of **105** could be protected, then metal-halogen exchange should provide a carbanion that would be acylated intramolecularly. A double bond could then be introduced to afford the cyclopentenedione **89**. Attempts to prepare a cyclic acetal from **105** using ethylene glycol, p-toluenesulfonic acid, and triethyl orthoformate resulted in substitution of chloride rather than protection of the ketone carbonyl, and ethyl ether **106** was isolated together with unreacted starting material. Evidently we had to replace the chlorine by another group which allows carbanion formation.



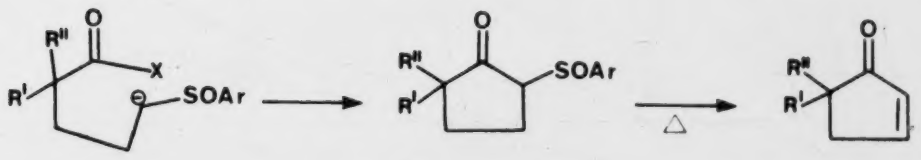
105



106

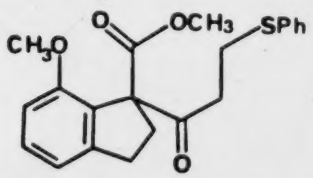
The report[68] of intramolecular acylation of α-sulfinyl carbanions **107** as a route to 5-substituted cyclopentenones of type **108** (Scheme 32) prompted us to try substitution reactions on **105** with sulfur nucleophiles.

Scheme 32

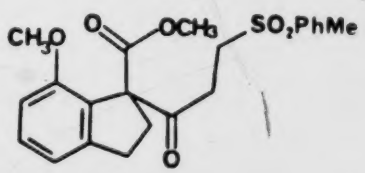


107 108

While reaction of chloride **105** with lithium thiophenoxide gave sulfide **109** in moderate yield (46%), reaction of **105** with sodium p-toluenesulfinate dihydrate to give **110** proceeded in excellent yield (93%).



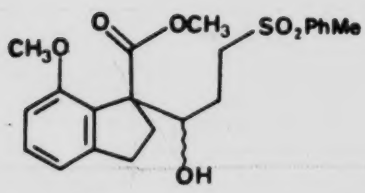
109



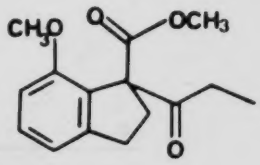
110

Sodium borohydride reduction of **110** gave β-hydroxyester **111** (70%) as an ca. 5:1 mixture of diastereoisomers, and β-ketoester **112** (12%). We could improve the overall yield markedly by condensing ester **70** with aldehyde **114** (Scheme 33) to directly give **111** (78%) as an ca. 1:1 mixture of diastereoisomers. Aldehyde **114** is a known compound[70] and was prepared from commercially available reagents: condensation of 3-chloropropionaldehyde diethyl acetal and sodium p-toluenesulfinate

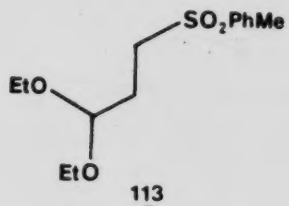
dihydrate gave **113** and hydrolysis of the acetal then afforded aldehyde **114**.



111



112

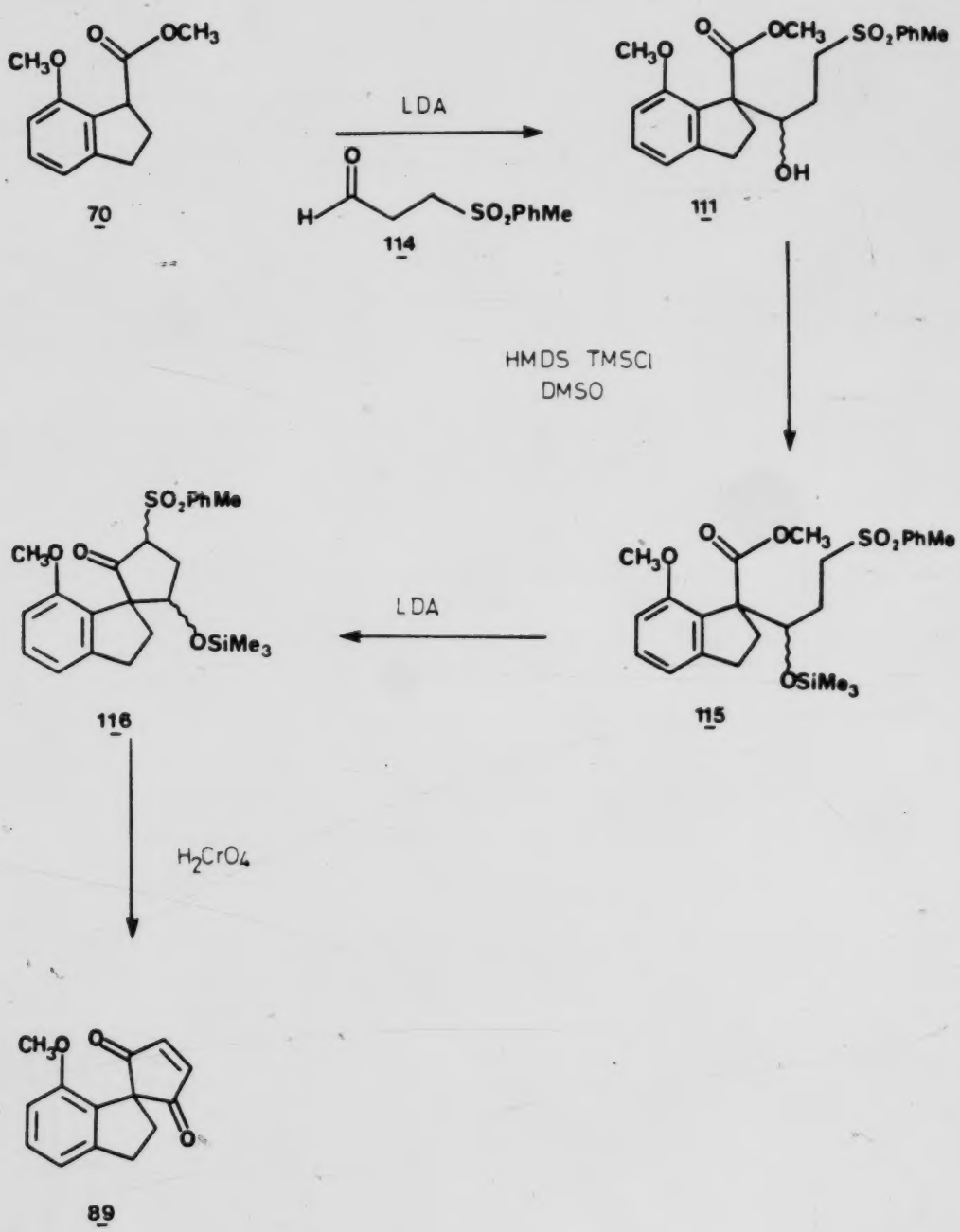


113

The hydroxyl group of **111** was protected[71] as its trimethylsilyl ether **115** (93%) (Scheme 33) and the product was treated[68] with LDA to prepare spirocyclopentane **116** as a mixture of diastereoisomers.

Treatment of **116** with Jones reagent[53] and subsequent chromatography of the crude reaction mixture over silica gel gave spirocyclopentenedione **89** in good yield (88%). Chromatography over silica gel appeared to be important in order to obtain high yields. This may be due to completion of the sulfone elimination on silica gel. Another point of interest with regard to this transformation is the reaction time, as a prolonged (t_R = 5 hours *cf.* t_R = 1.5 hours] exposure of **116** to chromic acid resulted in some degradation of material to 7-methoxyindanone. Now that we had a reasonably efficient route to spirocyclopentenedione **89** (54% overall yield from

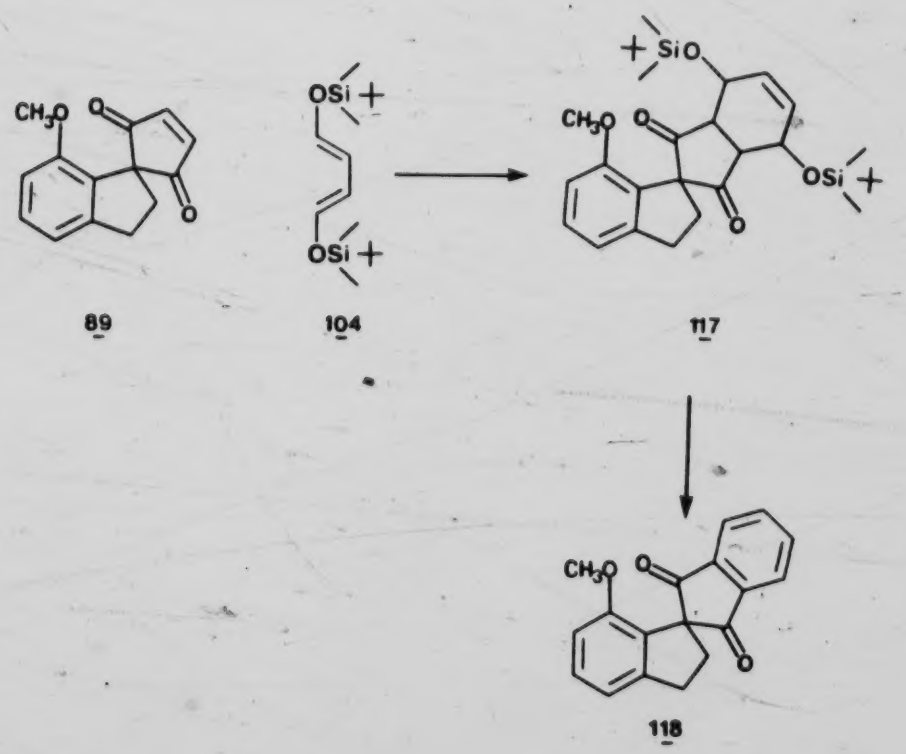
Scheme 33


CH3O
OCH3
O
70
LDA
H
O
SO2PhMe
114
OCH3
SO2PhMe
OH
111
HMDS TMSCl
DMSO
SO2PhMe
OSiMe3
115
LDA
SO2PhMe
OSiMe3
116
H2CrO4
89

ester **70**), we proceeded to study its Diels-Alder reaction with the oxygenated dienes **104**[67] and **77**.[56]

A thermal Diels-Alder reaction of bis-siloxybutadiene[67] **104** and ene-dione **89** gave a low yield (9%) of the tetracyclic spiro compound **118** (Scheme 34). This product presumably results from elimination of the tert-butyldimethylsiloxy groups in the initial Diels-Alder adduct **117**. Although most of the unreacted dienophile was recovered, the excess of diene decomposed under the reaction conditions (T = 140°C, 16 hours, under argon).

Scheme 34



89 **104** **117** **118**

Two of the standard techniques for improving the efficiency of Diels-Alder reactions are complexation of the reactants with Lewis acids or application of high pressure. We chose not to use Lewis acid catalysis due to the sensitive nature of dienes **104** and **77**, and instead considered the use of high pressure.[72,73]

The high pressure equipment* used for this experiment consisted of a Harwood High Pressure Intensifier (stroke 7", main cylinder diameter 2 1/2", piston diameter 5/8") attached to a domestically built high pressure oil line fitted with appropriate gauges and release valves. The pressure developed by the oil line was multiplied sixteen fold by the Harwood equipment (Imperial Oil hydraulic fluid Bayol 35 was used).

A dichloromethane solution of the reagents **89** and **104** was transferred to a small steel bellows[72] so as to completely fill the vessel, and the container was sealed with a copper washer and screw. The reaction vessel was subjected to a pressure of ca. 284,000 psi for 55 hours. Flash chromatography of the crude reaction mixture gave the Diels-Alder adduct **117** (48%) as a mixture of three [TLC and ^{1}H NMR] isomers. Although the isolated yield was

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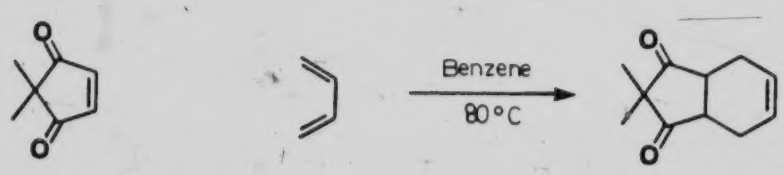
*I thank J. Ferch for assistance with the high pressure equipment.

low we felt that this was a consequence of the makeshift nature of the experimental procedure and does not accurately reflect the efficiency of this high pressure Diels-Alder reaction.

2,5-Bis-(trimethylsiloxy)furan **77** has been used in Diels-Alder reactions to prepare 1,4-dihydroxybenzene and 1,4-quinone adducts.[56] Attempts to react ene-dione **89** with furan **77** under thermal conditions were unsuccessful and unfortunately technical problems prevented us from trying this reaction under high pressure.

On the basis of electronic considerations we would expect ene-dione **89** to be a good dienophile and we believe that our Diels-Alder reaction is impeded by steric factors. For example, the disubstituted ene-dione **119** is known to react with butadiene at 80°C.[74]

Scheme 35



119

These considerations indicated that we should approach the spiro system by reactions that are less sensitive to steric factors and at this point a radical

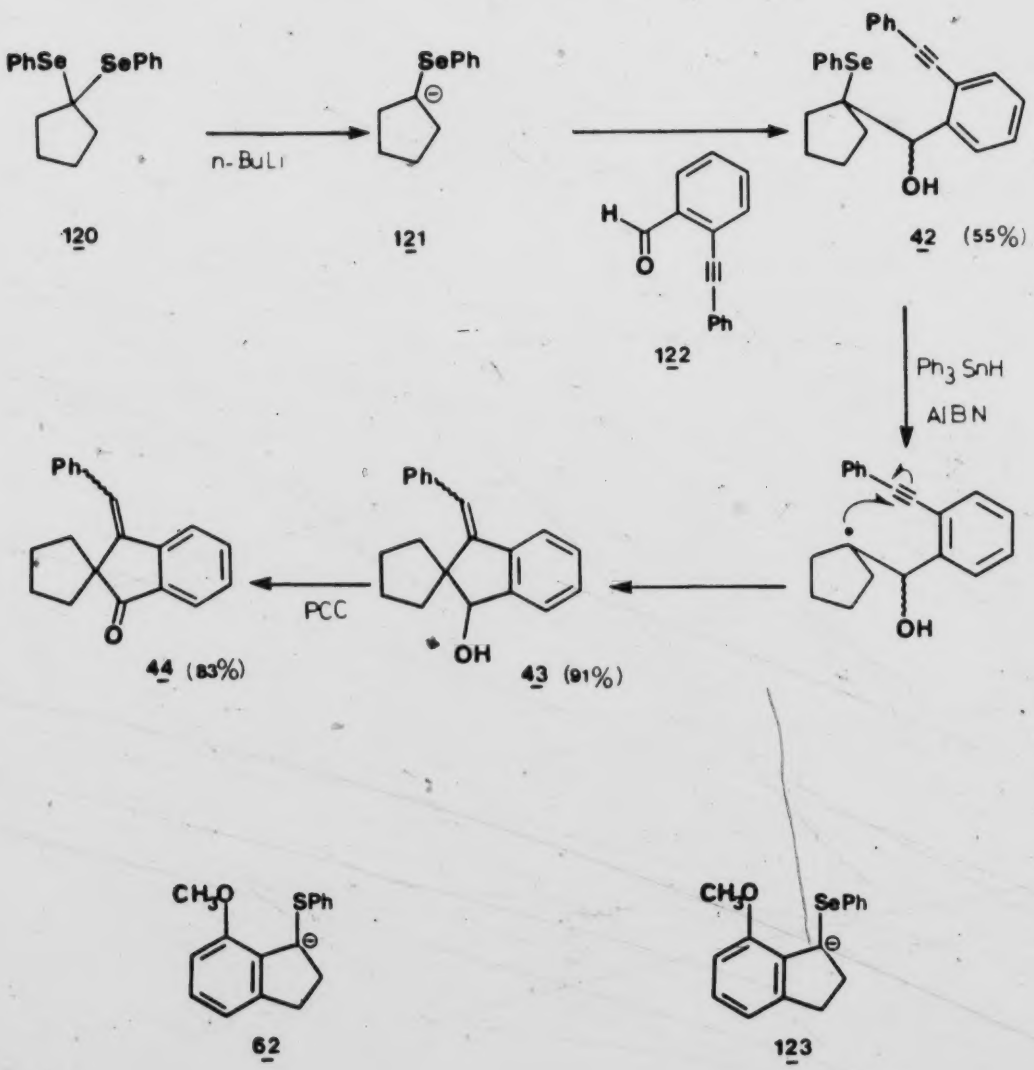
cyclization approach to spirocycles, that appeared to satisfy this requirement, had been developed in our laboratory. We decided to apply this new methodology to our case.

D. Synthesis of Spiro Compounds by Radical Cyclization

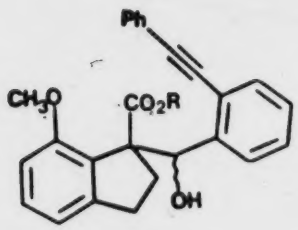
The procedure developed in our group for synthesis of carbocyclic spiro compounds is based on cyclization of an alkyl radical, in a 5-exo fashion, onto a triple bond (Scheme 36). Diselenoacetal **120** was treated with n-butyllithium to give α-selenocarbanion **121**. Acylation of **121** with aldehyde **122** and homolytic cleavage of the carbon-selenium bond of the resultant hydroxyselenide **42** gave the spiro[4,4]nonane **43**, and oxidation of the hydroxyl group afforded cyclopentanone **44**.

We were reluctant to use an α-selenocarbanion to form a quaternary carbon center because of our experience with the corresponding sulfur analogue **62**. Although we could prepare **62**, we failed to acylate it. It did not seem that experiments with the α-selenocarbanion **123** would be much more successful and so we considered a slightly different method of implementing the radical spirocyclization approach.

Scheme 36



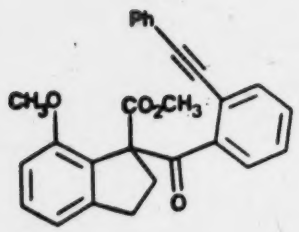
The dianion of acid **65** was acylated with aldehyde[43] **122** to give β-hydroxyacid **124** as a mixture of diastereoisomers in a ratio of ca. 1.3:1, in moderate yield (42%).



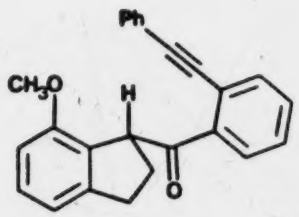
124 R=H
125 R=CH_3

Ester **70** on the other hand was condensed with **122** to give β-hydroxyester **125**, as a mixture of diastereoisomers in a ratio of ca. 9:1 in good yield (78%). Oxidation of **125** with Jones reagent[53] gave β-ketoester **126** (85%) but attempted preparation of ketone **127** by basic hydrolysis and subsequent decarboxylation of the β-ketoacid resulted in degradation of the molecule. Acid **65** was isolated from the reaction mixture and was formed evidently by attack of hydroxide at the ketone carbonyl followed by retroaldol reaction and, finally, ester hydrolysis. We did not examine the (conventional) use of acid hydrolysis of the β-ketoester **126** because in the meantime we had found a satisfactory route to the desired ketone **127**.

Ketone **127** was prepared (55%) by acylation of the dianion of acid **65** with acid chloride **130** (Scheme 37). 2-(Phenylethynyl)benzoyl chloride **130** was prepared from the corresponding acid **128**, which in turn was made either by



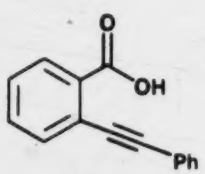
126



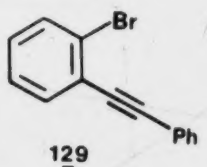
127

oxidation of aldehyde **122**[75] or from 2-bromodiphenylacetylene **129**.[75]

Deprotonation of ketone **127** (Scheme 37) and subsequent reaction with phenylselenenyl chloride[76] gave,



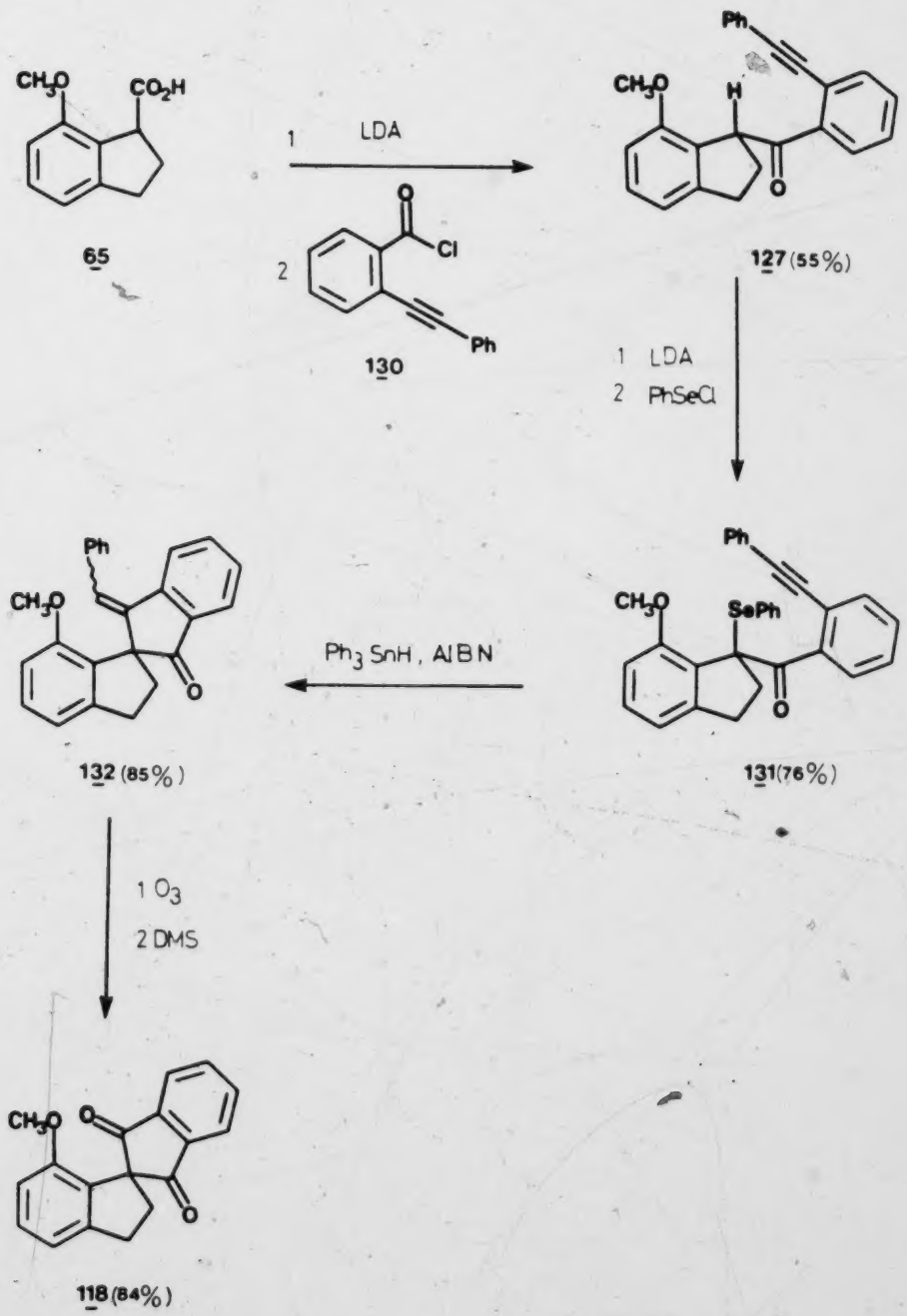
128



129

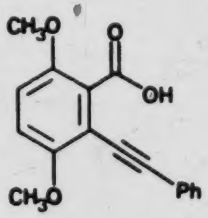
α-selenoketone **131** as an unstable oil. Addition of triphenyltin hydride and azobis(isobutyronitrile) to a refluxing benzene solution of **131** resulted in homolytic cleavage of the carbon selenium bond and cyclization of the resultant radical onto the triple bond.[32] Spirocyclopentanone **132** was formed in 84% yield as a mixture of diastereoisomers in a ratio of ca. 1:1. Ozonolysis of **132** gave the spiro tetracyclic compound **117**. This material proved to be identical with that obtained by the Diels-Alder route.

Scheme 37


CH3O
CO2H
65
1 LDA
2
Cl
O
Ph
130
Ph
CH3O
H
O
127 (55%)
1 LDA
2 PhSeCl
Ph
CH3O
SePh
O
131 (76%)
Ph3SnH, AIBN
Ph
CH3O
O
132 (85%)
1 O3
2 DMS
CH3O
O
O
118 (84%)

The series of reactions outlined in Scheme 37 illustrate the application of radical cyclization methodology to synthesis of relatively simple spiro compounds related to fredericamycin. We prepared dialkoxy and monoalkoxy analogues of acid **128** and evaluated them for use in a similar sequence.

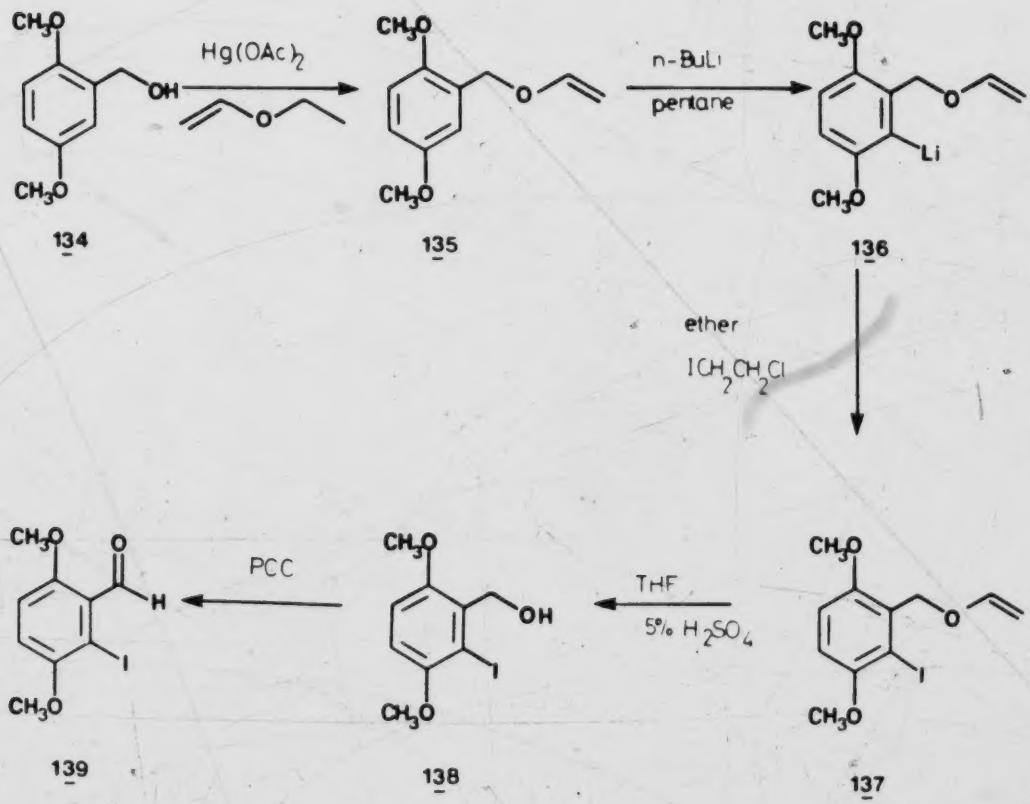
Our first target was 3,6-dimethoxy-2-(phenylethynyl)-benzoic acid **133**. We examined several different routes to this molecule; one of which involved use of heteroatom-mediated lithiation, another, use of Diels-Alder methodology, and a third was based on classical nitration and diazonium ion chemistry of aromatic compounds.



133

3,6-Dimethoxy-2-iodobenzaldehyde **139** is a known compound[77,78] and was prepared in five steps from 2,5-dimethoxybenzyl alcohol as outlined in Scheme 38. Although this is not a particularly efficient route to **139** (average overall yield of **139** from **134** in our hands was 11%) it does provide a compound which, in principle, can be converted to the desired acetylenic acid by two

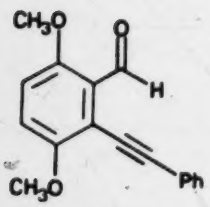
Scheme 38



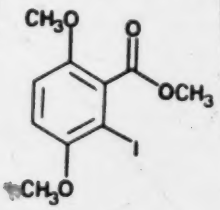
transformations, i.e. coupling with a copper(I) acetylide and oxidation of the aldehyde to the acid.

Iodo-aldehyde **139** was coupled with copper(I) phenylacetylide[79] to give **140** in poor yield (19%) but treatment of aldehyde **140** with Jones reagent[53] failed to give acid **133**. Oxidation of either alcohol **138** or aldehyde **139** and subsequent esterification with diazomethane gave methyl ester **141** in low yield (13%). In contrast to the iodo-aldehyde **139**, iodo-ester **141** was coupled with copper(I)

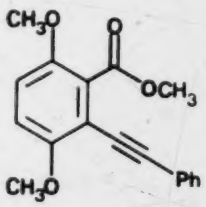
phenylacetylide[79] to give methyl 3,6-dimethoxy-2-(phenylethynyl)benzoate **142** in high yield (94%).



140

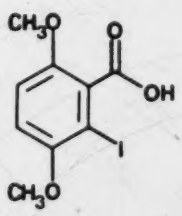


141



142

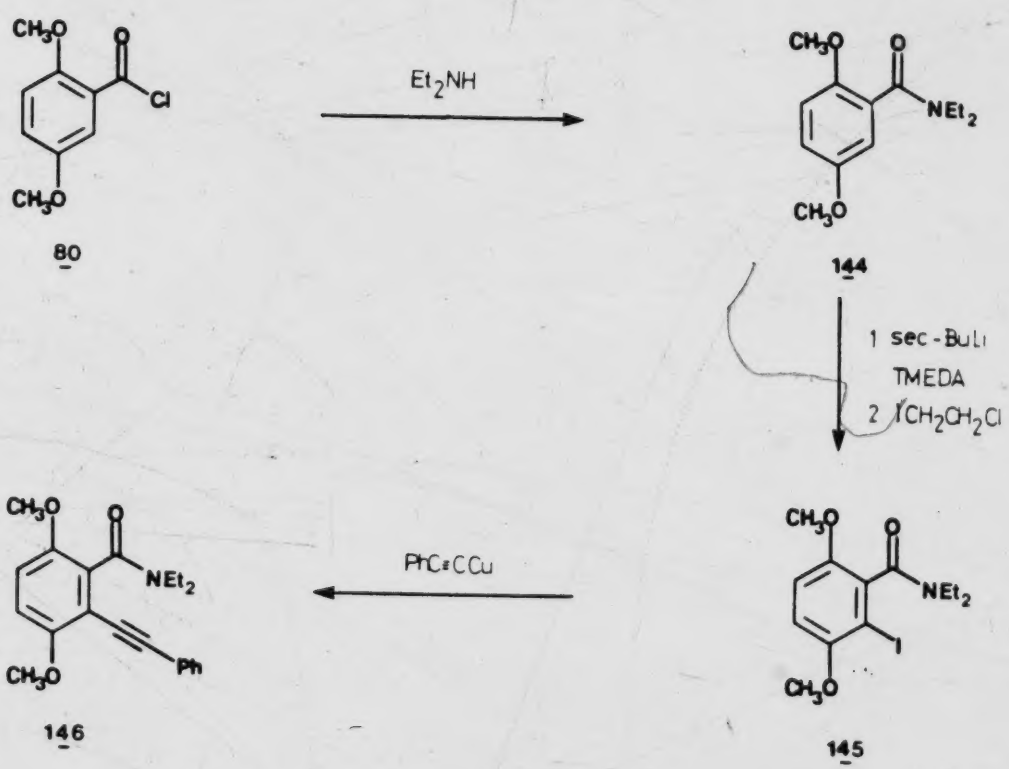
We also examined several other directing groups in the hope of improving our route to β-iodoester **141** or the corresponding acid **143**.



143

N,N-Diethyl benzamides have been found to be useful for synthesis of polysubstituted aromatics that are difficult to prepare by conventional methods[80,81] and so we investigated the following sequence. N,N,-Diethyl-2,5-dimethoxybenzamide[80] **144** was prepared (Scheme 39) from 2,5-dimethoxybenzoyl chloride **80** and ortho-lithiated according to the general literature procedure.[80,81] The

Scheme 39



organo-lithium species was converted to the 2-iodobenzamide **145** by reaction with 1-chloro-2-iodoethane.[78] When the lithiation was carried out at -78°C (1 hour) with 1.1 equivalents of both sec-butyllithium and TMEDA, then addition of 1-chloro-2-iodoethane gave a mixture of starting material and the desired product **145**. These compounds could not be separated by flash chromatography and so the mixture of

amides was treated with copper(I) phenylacetylide[79] to give the 3,6-dimethoxy-2-(phenylethynyl)benzamide **146** (56% overall yield) and the simple benzamide **144**. We subsequently found that by using slightly more sec-butyllithium and TMEDA (1.3 equivalents of each) and altering the reaction temperature, β-iodobenzamide **145** was obtained as a clean sample in high yield (98%).

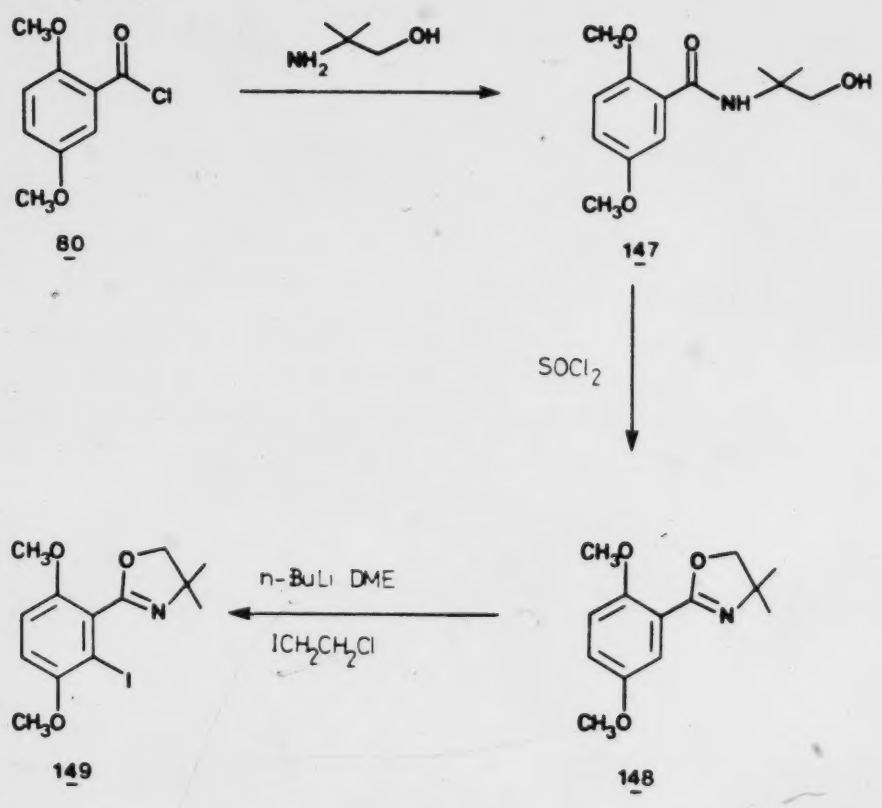
Tertiary amides are not especially good electrophiles although they have been used successfully in intramolecular acylations.[82] An attempt to condense dianion **71** with the (phenylethynyl)benzamide **146** was unsuccessful. We tried to hydrolyze amides **145** and **146**, but numerous attempts with aqueous acid,[80,83] anhydrous hydroxide[84] (KOtBu, H_2O and THF or ether) or trimethyloxonium tetrafluoroborate[85] were unsuccessful. In the reaction of **145** with Meerwein's salt we did observe some (22%) hydrolysis (after aqueous treatment) of the benzamide but this was accompanied by loss of iodine.

The failure to either condense or hydrolyze these tertiary amides prompted us to examine 2-(2,5-dimethoxyphenyl)-4,5-dihydro-4,4-dimethyl-2-oxazoline as an alternate starting material. Oxazolines,[86] while being poorer ortho-directing groups than diethylbenzamides,[87] should be more easily hydrolyzed to carboxylic acids.

A general procedure[88] was used to prepare oxazoline

148 from dimethoxybenzoyl chloride **80** and 2-amino-2-methylpropanol as outlined in Scheme 40.

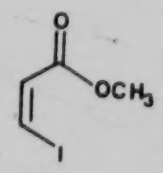
Scheme 40



The effect of solvent and base on aryl-metalation of the 3,5-dimethoxy analogue of **148** has been studied.[87] Either the ortho- or the para-lithiated species can be generated preferentially depending on the reaction conditions. Reaction of our oxazoline **148** with n-butyl-

lithium in DME[87] and subsequent addition of 1-chloro-2-iodoethane[78] gave the iodo product **149** in low yield (19%) along with unreacted starting material **148** (32% recovery). The poor yield of **149** made this an unacceptable route and we turned our attention to the Diels-Alder reaction of bis-siloxyfuran **77**[56] (Scheme 41) with an appropriate dienophile.

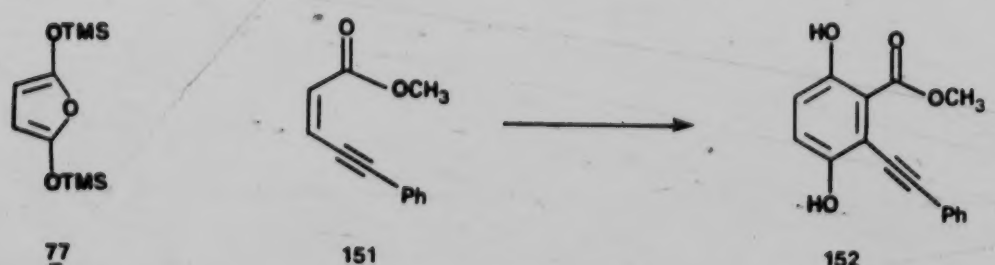
Methyl (Z)-3-(phenylethynyl)propenoate **151** was prepared from copper(I) phenylacetylide[79] and methyl (Z)-3-iodopropenoate **150**.[89] Diels-Alder reactions of **77** and **151**



150

proceeded in low yield to give, after aqueous work-up with fluoride, methyl 3,6-dihydroxy-2-(phenylethynyl)benzoate **152** (6%) and unreacted starting material **151** (70% recovery).

Scheme 41



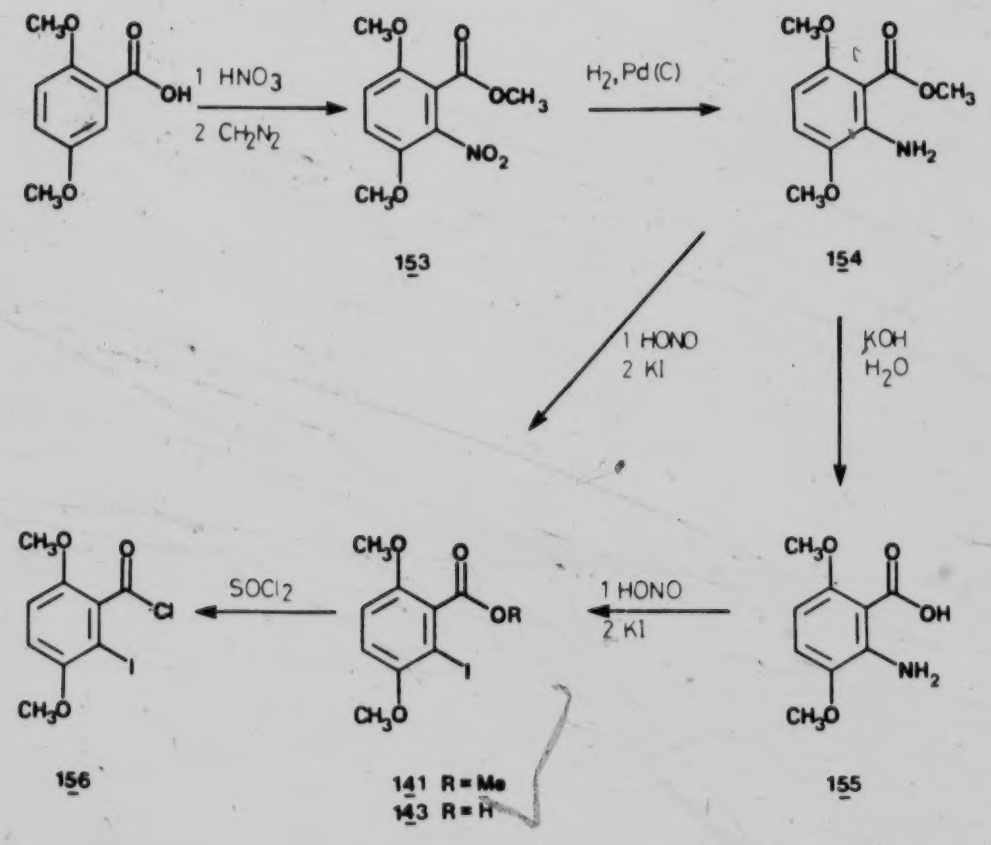
77 **151** **152**

The last and most successful method we explored for preparation of compounds of type **133** makes use of classical nitration and diazotization reactions of aromatic compounds (Scheme 42).

2,5-Dimethoxybenzoic acid was nitrated[90] and esterified to give nitro compound **153**. Reduction of the nitro group and hydrolysis of the ester afforded 2-amino-3,6-dimethoxybenzoic acid **155** which was converted, by a general procedure,[91] into 3,6-dimethoxy-2-iodobenzoic acid **143** (52%). Methyl ester **154** was likewise converted into the corresponding iodo compound **141** but, in the case of the ester, the nitration and Sandmeyer-type reaction with potassium iodide was not a reliable route to **141**, and we found the yields to vary from 16% to 48%. In addition, separation of product **141** from the simple reduction product (methyl 2,5-dimethoxybenzoate) proved to be tedious. We had previously found that conversion of 2-iodo-ester **141** into the 2-phenylethynyl derivative **142** was a high yield reaction (94%).

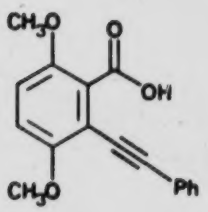
Hydrolysis of ester **142** on a small scale (0.31 mmol) with anhydrous hydroxide[84] gave acid **133** (53%) but attempts to carry out this reaction on a larger scale (0.71 mmol) led to a complex mixture of compounds. Intramolecular closure of the carboxylic acid onto the triple bond, to give a phthalide may be the source of the

Scheme 42



problems that we observed. When manipulation of acid **133** proved difficult we decided to study acylation reactions with esters **141** and **142**. Dianion **71** and ester **142** failed to react at 0°C or at room temperature and, on raising the temperature to 50°C, the ester function was partially converted into its N,N-diisopropylamide.

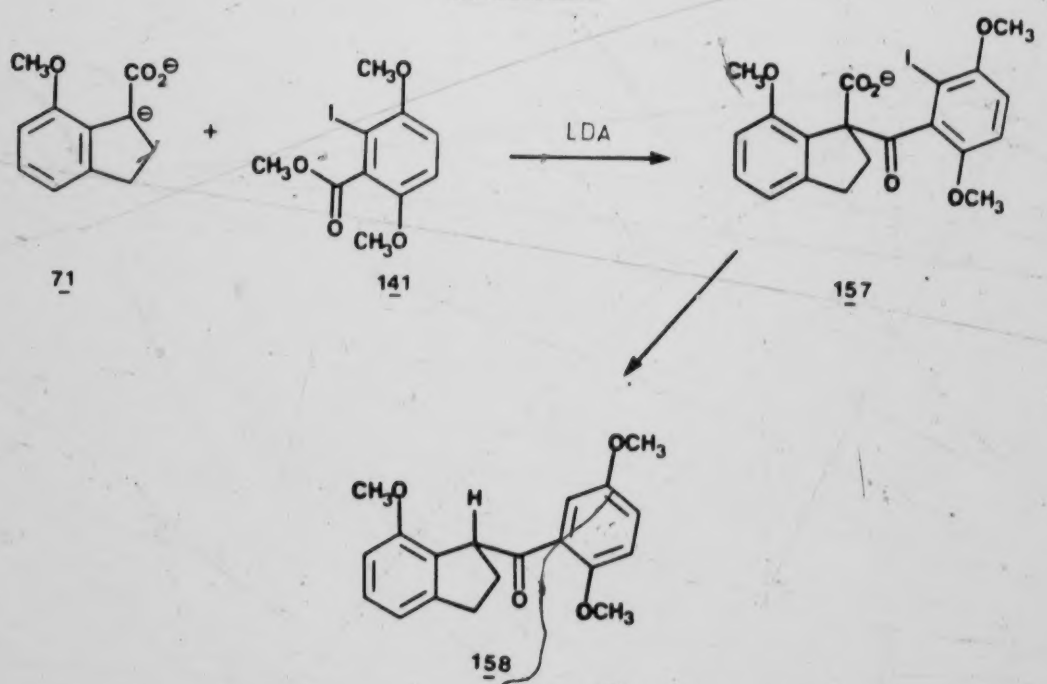
When a THF solution of dianion **71** and β-iodoester **141** (3.5 equivalents) was refluxed for 3 hours, unreacted



133

starting material **141** (91% recovery) and ketone **158** (12%) (Scheme 43) were isolated from the reaction mixture.

Scheme 43

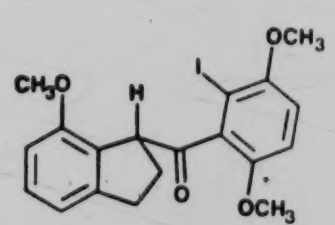


71 141 157 158

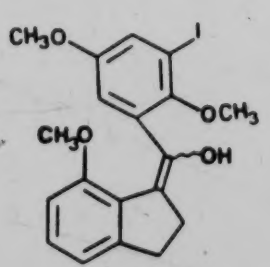
Ketone **158** may result from acylation of dianion **71** to give β-ketoacid **157** and subsequent metal-halogen exchange and decarboxylation to give the deiodinated ketone **158**. This

possibility prompted us to carry out the following experiment: Acid chloride **156** (Scheme 42), prepared from acid **143** and thionyl chloride, was added to carbanion **73.** An additional equivalent of LDA was injected and the mixture was stirred at room temperature overnight. Analysis of the reaction mixture by TLC and ^{1}H NMR showed this approach to be unpromising due to the many compounds formed.

Dianion **71** was next acylated with acid chloride **156** to give ketone **159** (27%) as a slightly impure sample whose ^{1}H NMR ($CDCl_3$, 400 MHz) spectrum showed the material to exist mainly as its enolic tautomer **160.** The low field singlet at δ9.22 suggests intramolecular hydrogen bonding of the hydroxyl proton with the methoxy substituent of the aromatic ring.



159

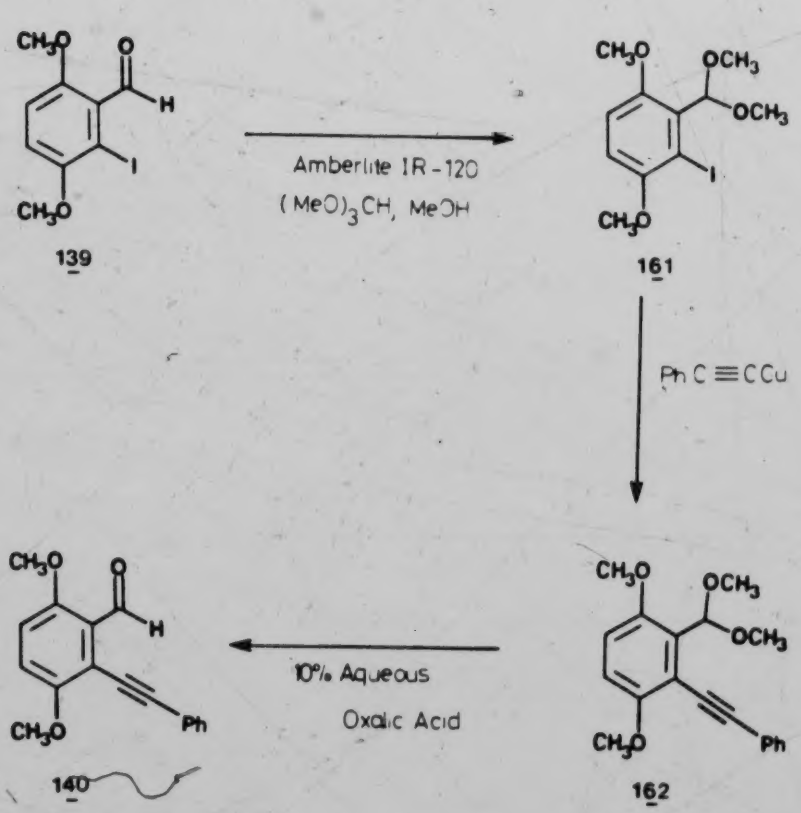


160

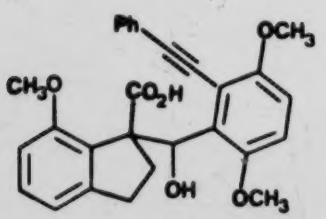
As esters **141, 142,** and acid chloride **156,** were evidently not ideal electrophiles, we decided to examine

aldehyde **140**. As we have already seen, the copper(I) phenylacetylide coupling reaction with 3,6-dimethoxy-2-iodobenzaldehyde proceeds in low yield (19%) to the corresponding 2-(phenylethynyl)-derivative. The yield of this transformation was markedly improved by protecting the aldehyde as a dimethyl acetal[92] (**161**) and then carrying out the coupling reaction. Finally, hydrolysis[93] of the acetal **162** gave 3,6-dimethoxy-2-(phenylethynyl)-benzaldehyde **140** in 55% overall yield (Scheme 44).

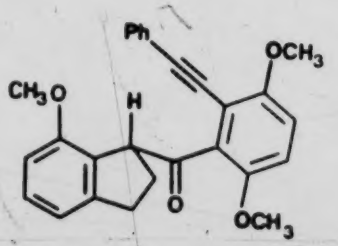
Scheme 44



Dianion **71** was acylated with aldehyde **140** to produce β-hydroxyacid **163** (29%) as a fairly insoluble solid.



163

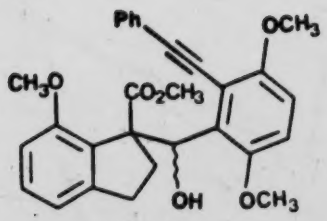


164

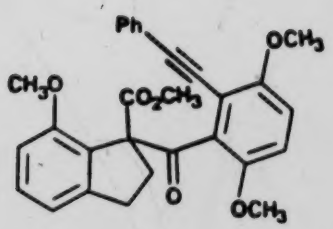
An attempt to oxidize **163** with pyridinium chlorochromate, so as to form **164** after decarboxylation of the intermediate β-ketoacid, led to degradation of the molecule. The retroaldol product **140** (25%) was the only major component detected in the reaction mixture. Exposure of **163** to manganese dioxide was also unsuccessful and unreacted β-hydroxyacid **163** was recovered.

At this stage the carbanion of ester **70** was acylated with aldehyde **140** to give β-hydroxyester **165** in moderate yield (55%). Pyridinium chlorochromate oxidation of **165** was a sluggish reaction and after 18 hours at room temperature β-ketoester **166** (30%) and unreacted starting material **165** (50%) were isolated.

In this series of experiments we had been able to join the 1-carboxyindane **65** and 1-carbomethoxyindane **70** to a 3,6-dimethoxy-2-(phenylethynyl)acyl unit, but the yields



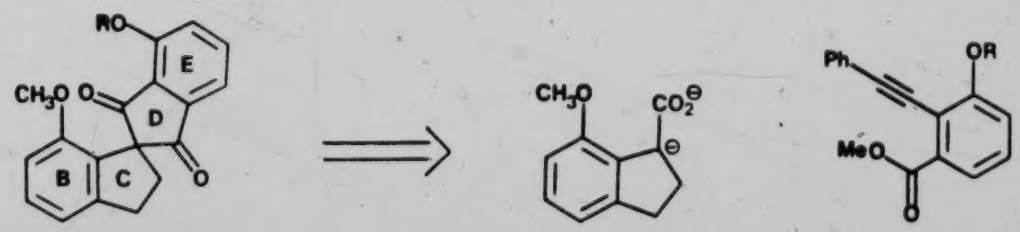
165



166

for the acylation reactions were generally low and the products were difficult to handle. The compounds we are trying to make are sterically conjested and it is possible that this fact is responsible for the problems we were experiencing. We decided, therefore, to study the monoalkoxy ester **168**.

Scheme 45



167 71 168

If the R group of **168** is suitably differentiated from the methoxy group of the indane moiety (**71**) it should be possible to deprotect ring E in the product **167**. A hydroxy group <u>para</u> to the resulting free hydroxyl in ring

E could then be introduced. This would set the stage for oxidation of ring E to a quinone and Diels-Alder reaction with an oxygenated diene would then give the skeleton we want for fredericamycin.

Accordingly, we set out to prepare acetylenic ester **178** (Scheme 46). The required precursor, 3-benzyloxy-2-iodobenzoic acid **177** is a known compound[91] and we made it by a slight modification of the literature procedure.[91]

meta-Cresol was nitrated* and methylated to give 3-methoxy-2-nitrotoluene **171**.[94] Permanganate oxidation of **171**[94] and subsequent deprotection of the methyl ether[91] afforded 3-hydroxy-2-nitrobenzoic acid **173** which was converted[95] into benzyl 3-benzyloxy-2-nitrobenzoate **174**. Basic hydrolysis of this benzyl ester gave acid **175**[91,95] and sodium dithionite reduction[91] of the nitro group provided the β-amino acid **176**. A modified Sandmeyer sequence[91] was then used to prepare 3-benzyloxy-2-iodobenzoic acid and the crude material was esterified and purified as its methyl ester **177**. Coupling of **177** with copper(I) phenylacetylide[79] proceeded smoothly to give methyl 3-benzyloxy-2-(phenylethynyl)benzoate **178** (90%).

Since hydrolysis of **178** with anhydrous hydroxide[84]

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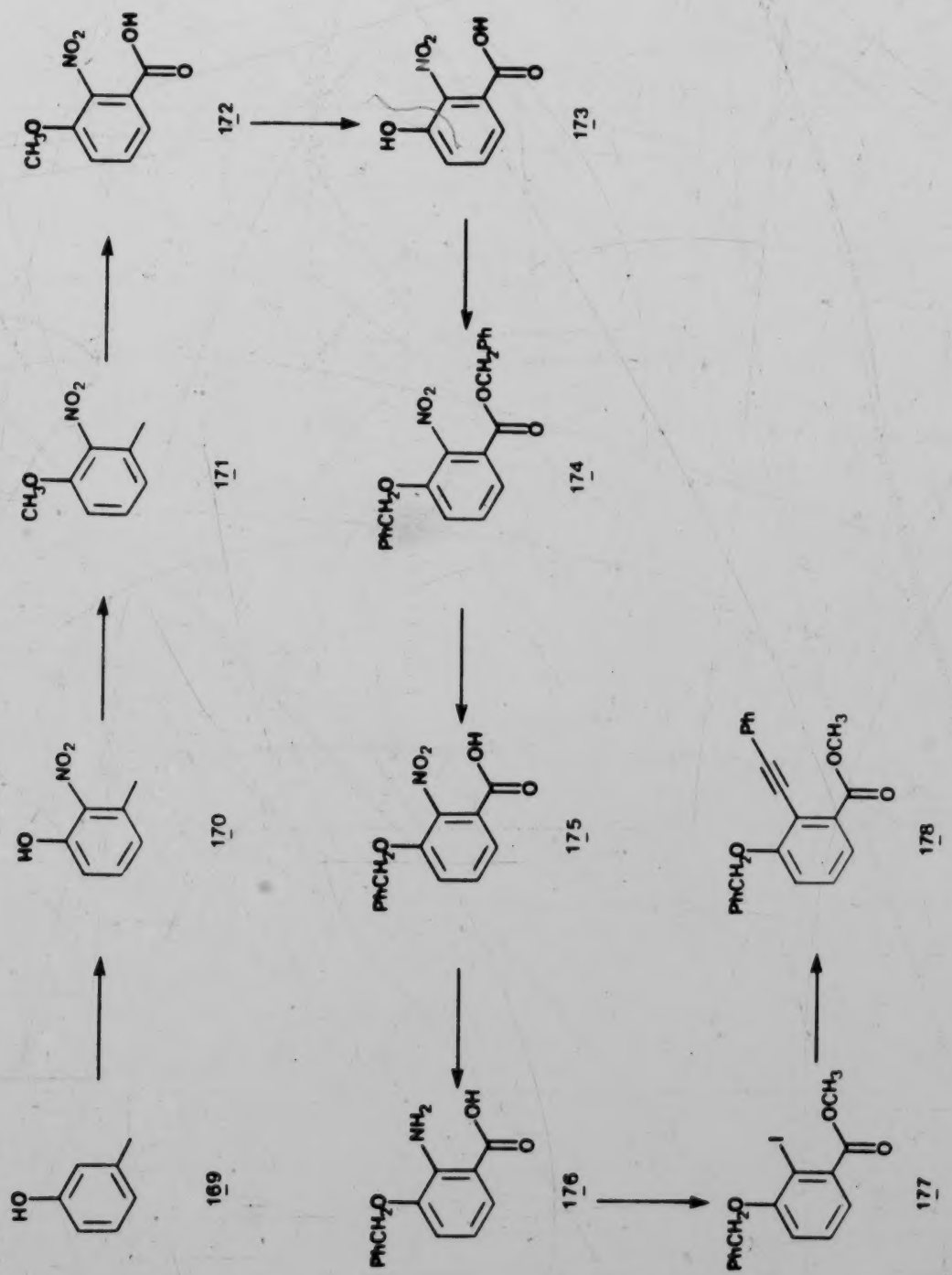
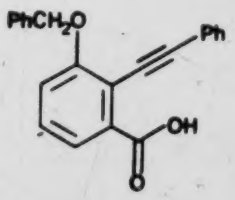
*Compound **170** was prepared by Dr. D.L.J. Clive according to the procedure of reference 94.

Scheme 46


HO
NO2
CH3O
OH
O
PhCH2O
OCH2Ph
NH2
I
OCH3
Ph
169
170
171
172
173
174
175
176
177
178

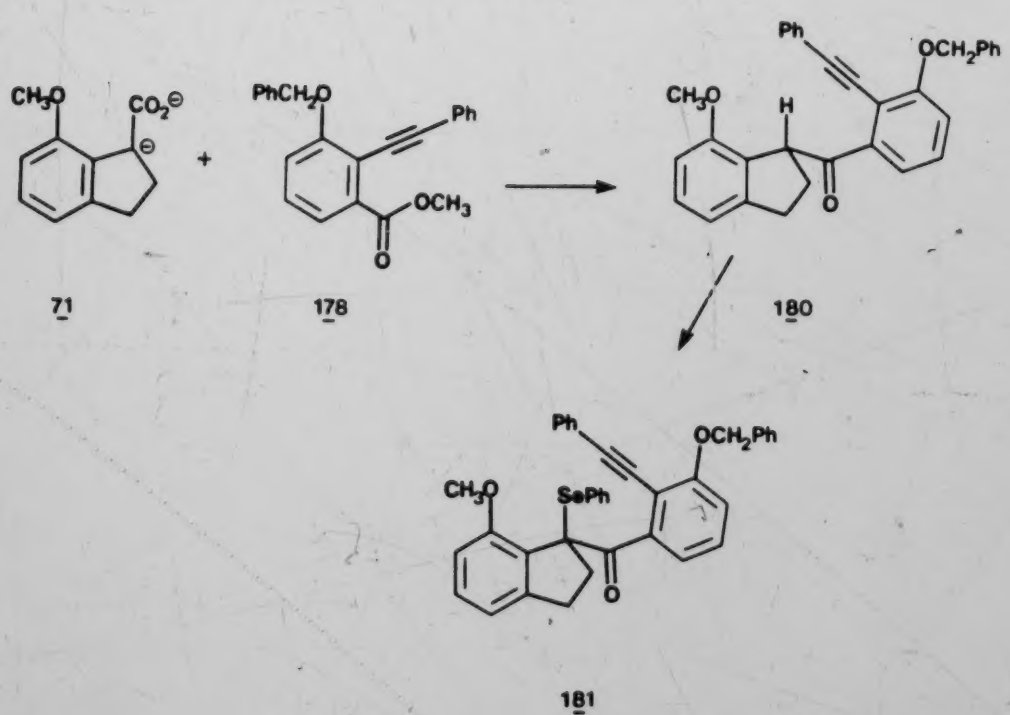
gave acid **179** in low yield (35%) we decided to study the acylation reaction of dianion **71** with ester **178**, rather than with the corresponding acid chloride of **179**.



179

Dianion **71** was condensed with the ester to give ketone **180** (Scheme 47). When the reaction is carried out

Scheme 47



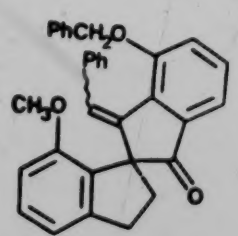
71 **178** **180**

181

at 50°C, then acylation followed by decarboxylation gives **180** in 39% overall yield. We found that addition of HMPA to the dianion solution, prior to addition of the ester, raised the yield of **180** to 51%. Ketone **180**, in contrast to ketone **159**, exists mainly in the keto form although the enol tautomer [characterized by signals at δ9.12(s) and δ4.02 (s)] was observed in the ^{1}H NMR spectrum of some samples.

The α-phenylseleno-ketone **181** was prepared (81%) in the conventional manner,[76] by deprotonation of **180** and addition of phenylselenenyl chloride.

The radical cyclization was done by slow addition of triphenyltin hydride and azobis(isobutyronitrile) to a refluxing benzene solution of **181**.[32] Flash chromatography of the reaction products over silica gel allowed a clean separation of the two major components A and B. The spectral data of these compounds were not consistent with our expectations for either the simple cyclized product **182** or the reduction product **180**.



182

The mass spectra of both A and B indicated that each had the same molecular formula, $C_{32}H_{26}O_3$. The fragmentation pattern of both compounds was the same and this suggested that A and B were isomeric. Along with the molecular ion (m/z 458, 100%), a prominent fragment at m/z, 278 for both A (90.5%) and B (97.0%) was observed. These values correspond to loss of $C_{14}H_{12}$ from the molecular ion. The Fourier transform infrared (FTIR) spectra of both compounds show carbonyl absorption [A (1720.0 cm^{-1}) and B (1718.5 cm^{-1})] characteristic of a five-membered ring conjugated ketone.

The NMR data for the major isomer (B) is summarized in Tables 1 and 2. A conspicuous feature of the ^1H NMR spectrum of B is the absence of a benzyloxy methylene singlet. This has been replaced by two low field doublets, each integrating for one proton, at δ5.24 and δ4.49. These two protons are <u>not</u> coupled to one another and <u>are</u> both coupled to a higher field proton at δ3.19. The broad signal in the aromatic region at δ6.53 was found to be coupled to signals at δ7.04 and δ6.80. The higher field ^{13}C signals are particularly diagnostic. Those at δ31.9 and δ32.4 are assigned to the methylenes of the indane moiety, and those at δ55.5 and δ66.7 correspond to a methoxy carbon and the quaternary center of the indane portion, respectively. The three doublets at δ86.1, 47.9 and 46.2 were of particular help in assigning the

Table 1. ^1H NMR of the Major Isomer of **187** (B).

δ	Multiplicity (J)	Integration	Assignment
7.41	m	2H	
7.16	m	4H	
7.04	m	3H	
6.93	t 7.5 Hz	1H	aromatic protons
6.80	t 7.5 Hz	2H	
6.66	d 8.0 Hz	1H	
6.53	d br ($W_{1/2}$=16 Hz) 6.0 Hz	2H	
6.41	d 7.5 Hz	1H	
5.24	d 10.0 Hz	1H	- H_1 of dihydropyran
4.49	d 12.0 Hz	1H	- H_3 of dihydropyran
3.76	s	3H	- methoxy protons
3.19	dd 10.0, 12.0 Hz	1H	- H_2 of dihydropyran
2.56	ddd 2.5, 9.0, 11.5 Hz	1H	
2.02	m	2H	indane protons
1.72	m	1H	

Table 2. ^{13}C NMR of the Major Isomer of 187 (B)

δ	Multiplicity	δ	Multiplicity
208.3	s	127.3	d
155.1	s	126.8	d
153.4	s	119.3	d
147.1	s	116.9	d
139.1	s	115.8	d
138.8	s	108.3	d
137.3	s	86.1	d
136.0	s	66.7	s
133.0	s	55.5	q
129.6	d	47.9	d
129.2	d	46.2	d
128.1	d	32.4	t
128.0	d	31.9	t
127.7	d		

structure of the cyclized product. The multiplicity of these carbon signals suggests that both the acetylene and the benzyloxy methylene of the starting material **181** have been involved in the transformations leading to the reaction product, and that neither functional group remains intact. On the basis of the spectra and the following chemical considerations we assign structure **187** (Scheme 48) to the product.*

If the α-keto radical **183** (Scheme 48) closes onto the acetylene in the usual 5-exo-fashion, the vinyl radical **184** would be generated. Normally such a radical will abstract hydrogen from the tin hydride that is present in the reaction mixture but, in this case our interpretation of the spectral data suggests hydrogen was abstracted from the benzyloxy methylene group in a 1,6 fashion to give the alkoxy radical **185**. This underwent 6-endo-closure as shown in Scheme 48. Finally, radical **186** abstracts hydrogen to give the observed product **187** (as a mixture of isomers).

We also interpret the spectral data of the minor compound, A, in terms of an isomer of structure **187**. The ^{1}H NMR spectrum shows a broad one proton singlet at δ5.46 and two one proton signals at δ3.56 (d, J = 6 Hz) and 3.39

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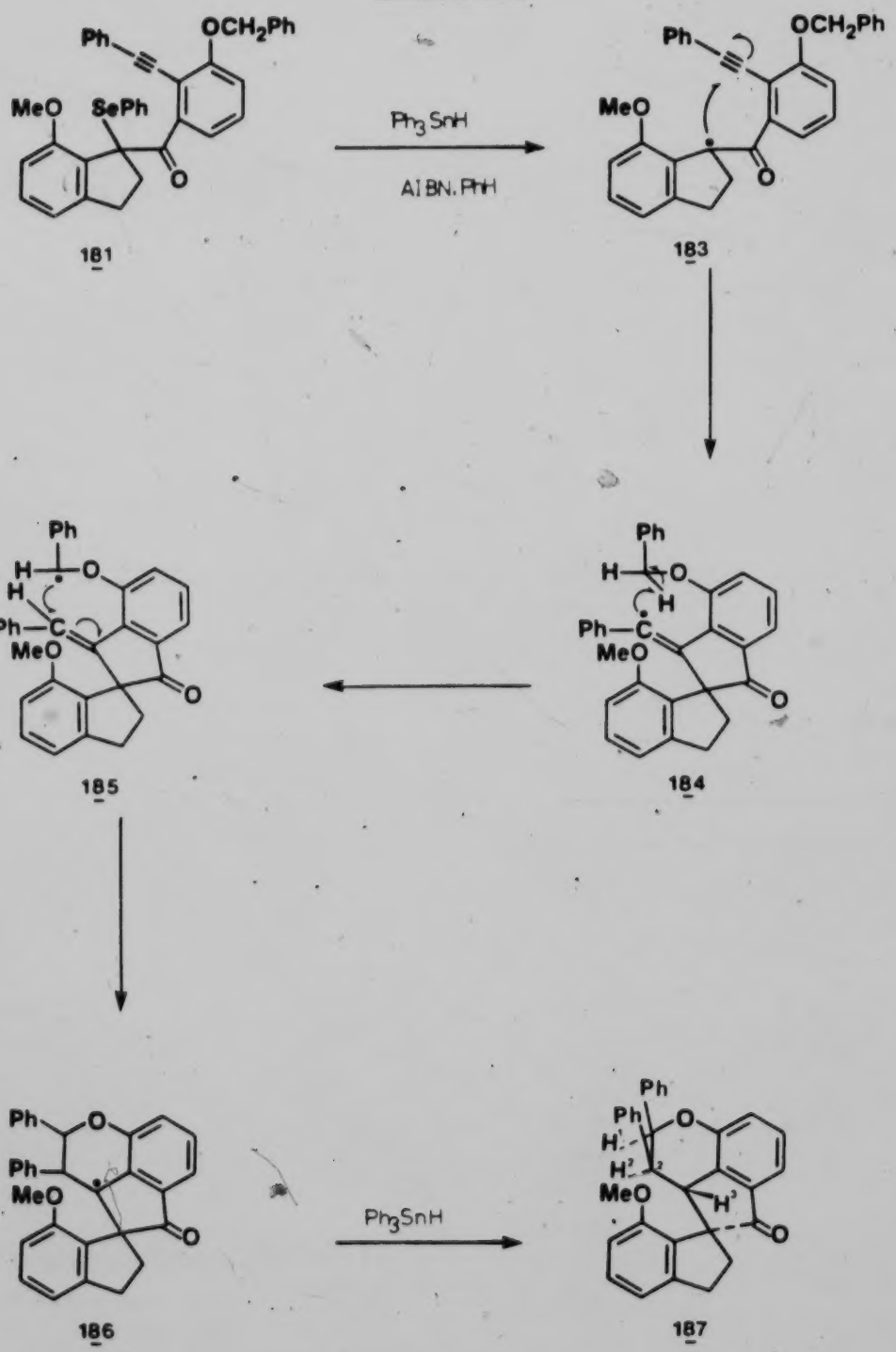
*We thank Dr. B. Dent and Dr. J. Sedgeworth for helpful discussions in assigning the structure **187**.

Scheme 48


Ph
OCH2Ph
MeO
SePh
O
Ph3SnH
AIBN.PhH
181
183
184
185
186
187
H
Ph
C
H1
H2
H3

(dd, J = 1.0, 6 Hz). The signals at δ3.56 and δ3.39 are coupled, and irradiation at δ3.39 causes both sharpening of the singlet at δ5.56 and collapse of the doublet at δ3.56. If the dihedral angle between H_1 and H_2 is near 90° then a small, or even zero, coupling between these protons is expected and on this basis we account for the broad singlet nature of the signal at δ5.46. The ^{13}C NMR spectrum of isomer A is similar to that of B with the exception of a downfield shift of one of the indane carbons [(δ41.4 and 32.4) in A and (δ32.4 and 31.9) in B]. The spectral data suggests that isomer A is the C-2 epimer of structure **187**.

The 1,6-hydrogen transfer is a very easy process and when the triphenyltin hydride and AIBN were added in one portion (as opposed to slow addition over 7 hours) to the α-selenoketone **181** we obtained the same two compounds. The major one (isomer B) in 89% yield and the minor one (isomer A) in 5.8% yield.

Although formation of **187** was not the result we had hoped for, this series of experiments does demonstrate the feasibility of preparing highly congested spiro systems by radical cyclization.

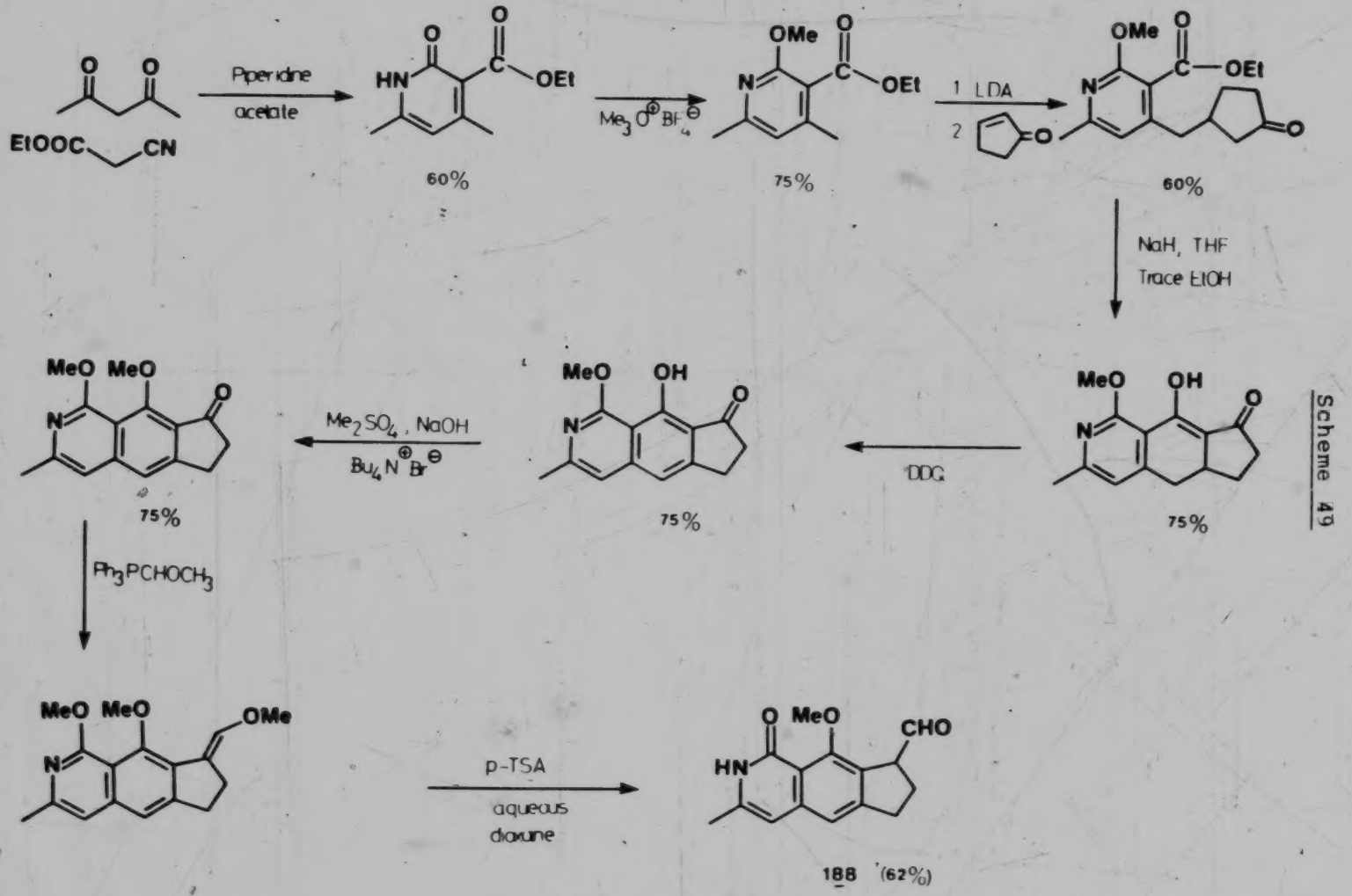
The synthesis of fredericamycin A is being continued in our group and the radical methodology is being applied to judiciously protected substrates in which the problems caused by the benzyloxy group are avoided.

In the above discussion no mention has been made of synthetic work on the isoquinoline segment of fredericamycin. This aspect of the problem has been studied by Dr. J. Sedgeworth and the route which has been developed to generate the isoquinoline compound **188** is shown in Scheme 49.

E. Conclusions

The results discussed in this thesis illustrate two successful approaches to spiro compounds related to fredericamycin. The first method is based on Diels-Alder chemistry and employs the use of high pressure conditions. The second route is based on a type of radical cyclization and appears to be the more synthetically useful method of the two. The radical cyclization technique is a very efficient process and was used to prepare sterically congested compounds. Because no completed synthesis of fredericamycin has yet been reported, it is difficult to compare the relative merit of our approach with those that have appeared in the literature. Unlike some of these other methods, however, the viability of our route in the presence of an indane methoxy group is clearly established and we do know that the new radical chemistry used here represents a technique of some generality.

The radical spiro cyclization route is the basis of current work towards the natural product in our laboratory.


Piperidine
acetate
60%
75%
1 LDA
2
60%
NaH, THF
Trace EtOH
75%
DDQ
75%
Me_2SO_4, NaOH
$Bu_4N^{\oplus}Br^{\ominus}$
75%
$Ph_3PCHOCH_3$
p-TSA
aqueous
dioxane
188 (62%)

Scheme 49

III. EXPERIMENTAL

General

Except where stated to the contrary, the following particulars apply: All apparatus was oven-dried overnight (140°C) and cooled in a desiccator over Drierite. Solvents for chromatography were distilled before use. Solvents for reactions were dried by distillation from a suitable drying agent under argon, and were transferred by oven-dried syringes. Reaction mixtures were stirred by use of Teflon coated magnetic stirring bars. During product isolation, solutions were dried with anhydrous magnesium sulfate and evaporated under water aspirator vacuum at 30°C. In those cases where compounds were isolated simply by evaporation of their solutions the residues were kept under oil-pump vacuum and checked for constancy of weight. The reported reaction yields are for homogeneous compounds (TLC, silica). Isolated products were either distilled or recrystallized for combustion analysis. Melting points (mp) were determined on a Kofler block melting point apparatus. Boiling points (bp) reported for products distilled in a Kugelrohr apparatus refer to the oven temperature. Commercial thin layer

chromatography (TLC) plates (silica gel Merck 60F-254) were used. Silica gel for flash column chromatography was Merck type 60 (230-400 mesh). TLC plates were examined under uv radiation (254 nm) and charred on a hot plate after being sprayed with either sulfuric acid (6 N in methanol) or phosphomolybdic acid [prepared from phosphomolybdic acid (3 g, $MoO_3 \cdot 2H_3PO_4 \cdot 48H_2O$) and ceric sulfate [0.5 g, $H_4Ce(SO_4)_4$] in 100 mL of 3% aqueous H_2SO_4]. Spinning band distillations were carried out on a Perkin-Elmer 151 annular still. Infrared (IR) spectra were recorded on a Perkin-Elmer 297 spectrophotometer or on a Nicolet 7000 FTIR model. Liquids were run as neat films on potassium chloride plates and solids were run either as solutions in carbon tetrachloride, using 0.5 mm potassium chloride cells, or as nujol mulls on potassium chloride plates. Absorbance peaks of at least 60% intensity of the strongest absorbance of a given spectrum are reported. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded with Bruker WP-80 (at 80 MHz), Bruker WP-200 (at 200 MHz), or Bruker WP-400 (at 400 MHz) spectrometers in the specified deuterated solvent with tetramethylsilane as an internal standard. The following abbreviations are used with respect to NMR spectra: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad; J = coupling constant; δ = chemical

shift. Mass spectra (MS) were recorded with A.E.I. model MS-12 (low resolution) or MS-50 (high resolution) mass spectrometers at an ionizing voltage of 70 eV. Chemical ionization (NH_3) mass spectra were run on an A.E.I. MS-12 instrument. Microanalyses were performed by the microanaytical laboratory of this department.

Materials

Dry dioxane, ether, and tetrahydrofuran (THF) were distilled immediately before use from sodium and benzophenone ketyl. Dry 1,2-dimethoxyethane (DME), diisopropylamine, triethylamine, dichloromethane, pyridine, chlorotrimethylsilane, and hexamethyldisilazane were distilled immediately before use from calcium hydride. Benzene, toluene, and xylene were distilled immediately before use from sodium. Dry hexamethylphosphoric triamide (HMPA), dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) were distilled from calcium hydride under reduced pressure (ca. 15 mm for HMPA and DMF and ca. 1 mm for DMSO) and stored over molecular sieves (3Å) under argon. N,N,N',N'-Tetramethylethylenediamine was distilled first from sodium hydroxide and then from calcium hydride, and dry methanol was distilled from magnesium. Commercial absolute ethanol was used without further purification.

Potassium tert-butoxide, (methoxymethyl)triphenylphosphonium chloride, 2,5-dimethoxybenzyl alcohol, 2,5-dimethoxybenzoic acid, tert-butyldimethylsilyl chloride, 3-chloropropionyl chloride, 3-chloropropionaldehyde diethyl acetal, diethyl maleate, pyridinium chlorochromate, manganese(IV) oxide, and phenylselenenyl chloride (all Aldrich materials) were used as received. 4-Indanol (Pfaltz and Bauer, Inc.), p-toluenesulfinic acid sodium salt (Eastman), (E,E)-1,4-diacetoxybuta-1,3-diene (Fluka), and azobis(isobutyronitrile) (AIBN) (Eastman) were also used without further purification.

The commercial solutions (Aldrich) of n-butyllithium in hexane, sec-butyllithium in cyclohexane, and tert-butyllithium in pentane were titrated before use, by the secondary butan-2-ol method[96] (2,2'-biquinoline was used as the indicator). Tetrabutylammonium fluoride was purchased as a 1 M solution in THF and used at the stated concentration.

2,3-Dihydro-4-methoxy-1H-indene (**56**)

Anhydrous potassium carbonate (872 mg, 6.31 mmol) was added to a solution of 4-indanol (770 mg, 5.74 mmol) and dimethyl sulfate (0.60 mL, 800 mg, 6.34 mmol) in acetone (20 mL, reagent grade). The mixture was refluxed for 24 h, cooled to room temperature, and filtered. The solid

was washed with acetone (*ca.* 40 mL) and the combined filtrates were evaporated and kept under oil pump vacuum for 1 h. Flash chromatography of the residue over silica gel (4 × 15 cm) with 7:1 hexane – ethyl acetate gave **56** (818 mg, 96%) as a colourless liquid: IR (film) 2955, 2840, 1585, 1480, 1465, 1260, 1075, 770 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ7.11 (t, J = 7.5 Hz, 1H), 6.85 (d, J = 7.5 Hz, 1H), 6.65 (d, J = 8.0 Hz, 1H), 3.81 (s, 3H), 2.89 (m, 4H), 2.06 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ156.3, 146.2, 131.8, 127.5, 116.9, 108.0, 55.2, 33.3, 29.5, 25.0; exact mass, m/z 148.0885 (calcd for $C_{10}H_{12}O$, m/z 148.0888).

Attempted deprotonation of 2,3-dihydro-4-methoxy-1*H*-indene (**56**)

a) *n*-Butyllithium (0.82 mL, 1.6 *M* in hexane, 1.31 mmol) was added dropwise over *ca.* 2 min to a solution of **56** (176.5 mg, 1.19 mmol) in cyclohexane[39] (3.0 mL) at room temperature, under nitrogen. The solution was stirred for 5 h and then quenched by addition of D_2O (*ca.* 0.5 mL). Water (*ca.* 10 mL) was added and the mixture was extracted with ether (2 × 20 mL). The combined extracts were washed with water (1 × *ca.* 10 mL) and brine (1 × *ca.* 10 mL), dried, and evaporated. The residue was identified (^1H NMR, 80 MHz) as unreacted starting material; there was no

evidence of deuterium incorporation.

b) t-Butyllithium (0.37 mL, 2 M in pentane, 0.74 mmol) was added dropwise over ca. 2 min to a solution of **56** (100 mg, 0.675 mmol) in cyclohexane (1.5 mL) at room temperature under nitrogen. Aliquots of the reaction mixture were removed at 3 h and 5 h time intervals and quenched with D_2O. The work-up was as described for the previous experiment. The ^1H NMR ($CDCl_3$, 80 MHz) spectrum for both samples showed only unreacted starting material; there was no evidence for deuterium incorporation.

Phenyl 3-chloropropionate (**57**)

Compound **57** (81.59 g, 88%) was prepared from phenol (47.15 g, 0.50 mol) and 3-chloropropionyl chloride (50.8 mL, 67.5 g, 0.55 mol), using the procedure of reference 40: bp 90-95°C (0.6 mm); IR (film) 1760, 1490, 1230, 1190, 1160, 1135, 755, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ7.18 (m, 5H), 3.75 (t, J = 7.5 Hz, 2H), 2.92 (t, J = 7.5 Hz, 2H); low resolution mass spectrum: m/z 186 ($M^{+\cdot}$, 2.5% of base peak) and 184 ($M^{+\cdot}$, 8.0% of base peak).

2,3-Dihydro-7-hydroxy-1H-inden-1-one (**58**)

Compound **58** (16.3 g, 25.1%) was prepared from phenyl 3-chloropropionate (**57**) (81.0 g, 0.44 mol) and aluminum chloride (293 g, 2.20 mol), using the procedure of

reference 40: mp 111-113°C; IR (CCl_4) 3330, 1680, 1618, 1600, 1465, 1345, 1298, 1288, 1200, 1158, 1055, 635 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ10.07 (s, 1H), 7.48 (t, J = 7.7 Hz, 1H), 6.95 (dd, J = 1.0, 7.0 Hz, 1H), 6.76 (dd, J = 0.5, 7.0 Hz, 1H), 3.10 (m, 2H), 2.71 (m, 2H). Upon D_2O exchange the signal at δ10.07 disappears. ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ209.8, 157.5, 155.1, 137.4, 122.6, 117.3, 113.3, 35.9, 25.8; low resolution mass spectrum: m/z, 148 ($M^{+\cdot}$, base peak).

2,3-Dihydro-7-methoxy-1H-inden-1-one (**59**)

Anhydrous potassium carbonate (2.82 g, 20.4 mmol) was added to a solution of hydroxyketone **58** (2.75 g, 18.6 mmol) and dimethyl sulfate (1.93 mL, 2.58 g, 20.4 mmol) in acetone (40 mL, reagent grade). The mixture was refluxed for 12 h, cooled to room temperature and filtered. The solid was washed with acetone (*ca.* 80 mL). The combined filtrates were evaporated and the residue was kept under oil pump vacuum for *ca.* 12 h to remove the excess of dimethyl sulfate. Flash chromatography of the residue over silica gel (5 × 15 cm) with 2:1 hexane – ethyl acetate gave **59** (2.81 g, 93%): mp 100-102°C; IR (CCl_4) 1710, 1590, 1475, 1298, 1274 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ7.56 (t, J = 7.75 Hz, 1H), 7.01 (dd, J = 1.0, 7.75 Hz, 1H), 6.78 (d, J = 8.5 Hz, 1H), 3.9 (s, 3H), 3.11 (m, 2H),

2.70 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ204.2, 158.1, 157.7, 136.1, 125.2, 118.3, 108.9, 55.6, 36.7, 25.4; exact mass, m/z 162.0673 (calcd for $C_{10}H_{10}O_2$, m/z 162.0681). Anal. calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 73.97; H, 6.17.

2,3-Dihydro-7-methoxy-1H-inden-1-ol (**60**)

Sodium borohydride (554 mg, 14.64 mmol) in anhydrous ethanol (20 mL) was added dropwise over 30 min to a cold (0°C) solution of ketone **59** (2.003 g, 12.35 mmol) in anhydrous ethanol (20 mL). The solution was then stirred at room temperature for 2 h and the mixture was quenched by addition of glacial acetic acid (1 mL). Water (ca. 40 mL) was added and the mixture was extracted with ether (2 × ca. 80 mL). The combined ether extracts were washed with water (1 × ca. 50 mL), 5% aqueous sodium bicarbonate (1 × ca. 50 mL) and brine (1 × ca. 50 mL), dried, and evaporated to afford alcohol **60** (1.359 g, 67%): mp 50-53°C; FTIR (CCl_4, cast) 3420, 1592, 1480.4, 1263.7, 1074.6 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ7.24 (t, J = 7.5 Hz, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 5.50 (m, 1H), 3.89 (s, 3H), 3.10 (ddd, J = 5.0, 8.5, 14.0 Hz, 1H), 2.83 (ddd, J = 6.0, 8.0, 15.0 Hz, 1H), 2.59 (d, J = 2.5 Hz, 1H), 2.45 (m, 1H), 2.04 (m, 1H). Upon D_2O exchange the doublet at δ2.58 disappeared and the

multiplet at δ5.50 sharpened to a doublet of doublets (J = 5.0, 7.0 Hz). ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ156.4, 145.5, 132.2, 129.8, 117.3, 107.9, 74.2, 55.0, 33.9, 30.3; exact mass, m/z 164.0832 (calcd for $C_{10}H_{12}O_2$, m/z 164.0837). Anal. calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.36; H, 7.38.

2,3-Dihydro-7-methoxy-1-(phenylthio)-1H-indene (**61**)

The general procedure of reference 44 was used: diphenyl disulfide (2.18 g, 10.0 mmol) and tri-n-butylphosphine (4.16 mL, 3.38 g, 16.7 mmol) were added to a solution of alcohol **60** (1.37 g, 8.34 mmol) in dry DMF (20 mL) under argon. The mixture was stirred at room temperature for 67 h, diluted with ether (ca. 250 mL), and extracted with 1 M NaOH (3 × ca. 100 mL). The ether layer was washed with water (1 × ca. 100 mL) and brine (1 × ca. 100 mL), dried, and evaporated. Flash chromatography of the residue twice over silica gel (5 × 15 cm) with 8:1 hexane – ethyl acetate gave **61** (1.206 g, 56.4%) as an oil which solidified upon standing: mp 75-79°C; IR (CCl_4) 1585, 1480, 1438, 1265, 1073, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ7.38 (m, 2H), 7.23 (m, 4H), 6.83 (d, J = 7.5 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 4.90 (d, J = 6.5 Hz, 1H), 3.84 (s, 3H), 3.06 (m, 1H), 2.78 (ddd, J = 1.0, 7.5, 15.5 Hz, 1H), 2.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ156.4

(s), 146.4 (s), 136.7 (s), 131.5 (d), 130.1 (s), 130.8 (s), 129.6 (d), 128.6 (d), 126.4 (d), 117.0 (d), 108.6 (d), 55.4 (q), 49.7 (d), 33.9 (t), 30.9 (t); exact mass, m/z 256.0921 (calcd for $C_{16}H_{16}OS$, m/z 256.0921). Anal. calcd for $C_{16}H_{16}OS$: C, 74.96; H, 6.29; S, 12.51. Found: C, 74.82; H, 6.25; S, 12.44.

Preparation and deuterium oxide quench of 2,3-dihydro-1-lithio-7-methoxy-1-(phenylthio)-1H-indene **62**

sec-Butyllithium (0.414 mL, 1.24 M in cyclohexane, 0.513 mmol) was added dropwise over ca. 10 min to a cold (-78°C) solution of sulfide **61** (88.5 mg, 0.345 mmol) in THF (3.0 mL) under argon. The reaction mixture was stirred at -78°C for 3 h, and then D_2O was added and stirring was continued at room temperature for 1 h. Dilute hydrochloric acid (ca. 15 mL, 1 M) was added and the mixture was extracted with ether (2 × ca. 15 mL). The combined extracts were washed with water (1 × ca. 10 mL) and brine (1 × ca. 10 mL), dried, and evaporated. The ^1H NMR spectrum of the crude residue showed complete incorporation of deuterium at the C-1 position. ^1H NMR ($CDCl_3$, 80 MHz) δ 7.30 (m, 6H), 6.75 (overlapping doublets; J = 8.0 Hz, 2H), 3.85 (s, 3H), 3.0 (m, 2H), 2.45 (m, 2H).

Attempted alkylation and acylation of 2,3-dihydro-1-lithio-7-methoxy-1-(phenylthio)-1H-indene **62**

a) A solution of benzaldehyde (0.23 mL, 0.984 mM in THF, 0.226 mmol) was added dropwise over ca. 2 min to a cold (-78°C) solution of carbanion **62** [prepared from **61** (39.0 mg, 0.152 mmol) and sec-butyllithium (0.184 mL, 1.24 M in cyclohexane, 0.228 mmol) in THF (1.5 mL)] under nitrogen. The mixture was stirred at -78°C for 30 min and at room temperature for 1.5 h. It was quenched by addition of several drops of glacial acetic acid. Water (ca. 10 mL) was added and the mixture was extracted with ether (2 × ca. 15 mL). The combined extracts were washed with water (2 × ca. 10 mL) and brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm) with 7:1 hexane – ethyl acetate allowed recovery of unreacted starting material **61** (22.4 mg, 57% recovery) as the only major reaction component.

b) A solution of benzoyl chloride (0.27 mL, 0.86 M in THF, 0.23 mmol) was added dropwise over ca. 2 min to a cold (-78°C) solution of carbanion **62** [prepared from **61** (20.0 mg, 0.0780 mmol) and sec-butyllithium (0.094 mL, 1.24 M in cyclohexane, 0.12 mmol) in THF (1.5 mL)] under nitrogen. The solution was stirred at room temperature for 3 h and then quenched by addition of dilute

hydrochloric acid (ca. 10 mL, 1 M). The mixture was worked up as described in the previous experiment. Flash chromatography of the residue over silica gel (1 × 15 cm) with 7:1 hexane – ethyl acetate allowed recovery of unreacted starting material **61** (12.0 mg, 60% recovery).

2,3-Dihydro-1-hydroxy-7-methoxy-1H-indene-1-carbaldehyde 1,3-dithiopropyl acetal (**66**)

n-Butyllithium (2.68 mL, 0.85 M in hexane, 2.28 mmol) was added dropwise over 15 min to a cold (-78°C) solution of dithiane (261 mg, 2.17 mmol) in THF (20 mL) under argon. The mixture was allowed to warm to -20°C over a 3 h period and was then cooled to -78°C. A solution of ketone **59** (356 mg, 2.19 mmol) in THF (10 mL) was then added dropwise over 1 h. The reaction mixture was allowed to warm up to room temperature over 1 h and was then quenched by addition of glacial acetic acid (0.5 mL). Water (ca. 30 mL) was added and the mixture was extracted with ether (2 × ca. 30 mL). The combined ether extracts were washed with 5% aqueous sodium bicarbonate (1 × ca. 30 mL) and brine (1 × ca. 30 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm) with 2:1 hexane – ethyl acetate gave **66** (0.26 g, 42%): mp 138°C; IR (CCl_4) 3570, 1475, 1255, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.23 (t, J = 7.8 Hz, 1H), 6.81 (d, J

= 7.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 5.06 (s, 1H), 3.89 (s, 3H), 3.26 (s, 1H), 2.97 (m, 2H), 2.80 (m, 5H), 2.10 (m, 2H), 1.81 (m, 1H). Upon D_2O exchange the signal at δ3.26 disappeared. ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ156.3, 145.9, 130.6, 130.4, 117.6, 108.5, 86.6, 57.9, 55.1, 36.3, 30.8, 30.5, 30.3, 25.9; exact mass, m/z 282.0744 (calcd for $C_{14}H_{18}O_2S_2$, m/z 282.0748). Anal. calcd for $C_{14}H_{18}O_2S_2$: C, 59.54; H, 6.42; S, 22.71. Found: C, 59.42; H, 6.53; S, 22.84.

4-Methoxy-1H-indene-3-carbaldehyde 1,3-dithiopropyl acetal (67)

a) p-Toluenesulfonic acid monohydrate (277 mg, 1.45 mmol) was added to a stirred solution of alcohol **66** (88.3 mg, 0.3126 mmol) in benzene (2.0 mL) at room temperature. After 2 h, ether (ca. 10 mL) was added and the mixture was filtered to remove the undissolved p-toluenesulfonic acid. The filtrate was washed with 5% aqueous sodium bicarbonate (2 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm) with 6:1 hexane – ethyl acetate gave **67** (65.2 mg, 78.9%) as a white solid: mp 126-128°C; IR (CCl_4) 1598, 1478, 1282, 1262, 1120, 1082, 910 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ7.16 (t, J = 8.0 Hz, 1H), 7.06 (dd, J = 1.0, 7.5 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.65 (m,

1H), 5.75 (s, 1H), 3.84 (s, 3H), 3.38 (d, J = 0.5 Hz, 2H), 3.05 (m, 2H), 2.92 (ddd, J = 14, 4.5, 3.0 Hz, 2H), 2.17 (m, 1H), 1.96 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ154.4, 146.3, 142.7, 131.3, 130.7, 126.4, 117.1, 109.4, 55.8, 45.1, 38.4, 31.8, 25.8; exact mass, m/z 264.0639 (calcd for $C_{14}H_{16}OS_2$, m/z 264.0643). Anal. calcd for $C_{14}H_{16}OS_2$: C, 63.60; H, 6.10; S, 24.25. Found: C, 63.83; H, 6.15; S, 23.75.

b) Alcohol **66** (104 mg, 0.368 mmol) in THF (4 mL) was added to a cold (0°C) solution of thionyl chloride (0.032 mL, 48 mg, 0.40 mmol) in pyridine (1.0 mL). The solution was stirred at room temperature for 1.5 h. Water (ca. 10 mL) was added and the mixture was extracted with ether (2 × ca. 15 mL). The combined extracts were washed with dilute hydrochloric acid (1 × ca. 10 mL), 5% aqueous sodium bicarbonate (1 × ca. 10 mL) and brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm) with 2:1 hexane – ethyl acetate allowed separation of olefin **67** (23 mg, 24%) and starting material **66** (39 mg, 37%).

Attempted reduction of 4-methoxy-1H-indene-3-carbaldehyde 1,3-dithiopropyl acetal (**67**)

a) Alkene **67** (11.0 mg, 0.0416 mmol) in degassed benzene (1.0 mL plus 1.0 mL rinse) was added to a stirred

suspension of tris(triphenylphosphine)rhodium(I) chloride (6 mg) in degassed benzene (0.5 mL) under hydrogen. The flask was flushed with hydrogen and maintained at a pressure of 10 psi for 11 h. The solvent was evaporated, and hexane (ca. 5 mL plus 5 mL rinse) was added. The mixture was filtered through a pad of Florisil and the filtrate was evaporated. Analysis [TLC (silica, 1:1 hexane – ethyl acetate, R_f = 0.65) and ^1H NMR ($CDCl_3$, 200 MHz)] of the residue showed only the presence of starting material **67**.

b) A mixture of alkene **67** (13.6 mg, 0.0514 mmol) and 5% palladium on charcoal (5.3 mg) in ethyl acetate (3 mL) was stirred for 13 h at room temperature at 10 psi. Analysis [TLC, silica, 1:1 hexane – ethyl acetate, R_f = 0.65] of the reaction mixture showed mainly starting material along with a trace of another component (R_f = 0.40). Additional catalyst (ca. 5 mg) and solvent (1 mL) were added and stirring was continued under an atmosphere of hydrogen (10 psi) for 9 h. Analysis [TLC] of the reaction mixture again showed mainly starting material.

c) Borane in THF (1.40 mL, 0.37 M in hydride, 0.518 mmol) was added dropwise over ca. 30 min to a cold (0°C) solution of alkene **67** (91.0 mg, 0.344 mmol) in THF (2.0 mL) under nitrogen. The mixture was stirred at 0°C for an additional 2.5 h and was then quenched by addition of

dilute hydrochloric acid (ca. 3 mL, 1 M) and water (ca. 10 mL). The aqueous layer was extracted with ether (2 × ca. 15 mL) and the combined extracts were washed with water (1 × ca. 10 mL), and brine (1 × ca. 10 mL), dried, and evaporated. Analyses of the residue [TLC (silica, 1:1 hexane – ethyl acetate, R_f = 0.65) and ^1H NMR ($CDCl_3$, 80 MHz)] showed only the presence of starting material **67**.

2,3-Dihydro-7-methoxy-1-(methoxymethylene)-1H-indene (**68**) and 2,3-Dihydro-7-methoxy-1H-indene-1-carbaldehyde (**69**)

The general procedure of reference 52 was used: potassium t-butoxide (3.47 g, 30.9 mmol) was added over 30 min, via a side arm addition funnel, to a suspension of (methoxymethyl)triphenylphosphonium chloride (10.59 g, 30.9 mmol) in dioxane (75 mL) under argon. The mixture was stirred at room temperature for 1.5 h, and then a solution of ketone **59** (2.00 g, 12.4 mmol) in dioxane (10.0 mL plus 5.0 mL rinse) was added over ca. 5 min. Stirring at room temperature was continued for 22 h. Water (ca. 50 mL) was then added and the aqueous solution was extracted with ether (2 × ca. 100 mL). The combined extracts were washed with brine (1 × ca. 50 mL), dried, and evaporated. The residue was dissolved in 2:1 hexane – ethyl acetate which contained just enough dichloromethane to dissolve the triphenylphosphine oxide. The solution

was loaded onto a column of silica gel (10 × 5 cm) and the column was developed with 2:1 hexane – ethyl acetate. This procedure allowed separation of the bulk of triphenylphosphine oxide from enol ethers **68**. The crude product was used directly in the preparation of aldehyde **69**.

A small amount of **68** was further purified by flash chromatography over silica gel with 5:1 hexane – ethyl acetate: Lower R_f isomer: IR (CCl_4) 2950, 2930, 2905, 2835, 1670, 1475, 1460, 1295, 1265, 1235, 1148, 1122, 1090, 1072 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ7.12 (t, J = 7.7 Hz, 1H), 6.85 (dd, J = 1.0, 7.4 Hz, 1H), 6.74 (d, J = 8.2 Hz, 1H), 6.11 (t, J = 1.6 Hz, 1H), 3.85 (s, 3H), 3.70 (s, 3H), 2.84 (m, 2H), 2.61 (m, 2H); exact mass, m/z 190.0996 (calcd for $C_{12}H_{14}O_2$, m/z 190.0994). Higher R_f isomer: ^1H NMR ($CDCl_3$, 200 MHz) δ7.04 (m, 2H), 6.84 (dd, J = 1.0, 7.5 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 3.90 (s, 3H), 3.75 (s, 3H), 3.00 (m, 2H), 2.79 (m, 2H). Mixture of both isomers: ^{13}C NMR ($CDCl_3$, 22.63 MHz) δ155.1, 147.2, 143.7, 139.2, 128.3, 128.2, 126.5, 121.1, 117.4, 110.3, 108.0, 60.2, 59.9, 56.0, 55.0, 31.5, 31.1, 30.5, 26.1.*

p-Toluenesulfonic acid monohydrate (300 mg, 1.58 mmol) was added to a solution of the crude enol ether **68**

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*Not all of the carbon signals of both isomers were resolved in this spectrum.

in aqueous dioxane (30 mL dioxane plus 10 mL water) and the mixture was stirred under reflux for 14 h. It was then cooled to room temperature, water (ca. 20 mL) was added, and the aqueous solution was extracted with ether (2 × ca. 80 mL). The combined extracts were washed with 5% aqueous sodium bicarbonate (1 × ca. 30 mL) and brine (1 × ca. 30 mL), dried, and evaporated. Flash chromatography of the residue twice over silica gel (5 × 15 cm) with 6:1 hexane – ethyl acetate gave **69** (1.740 g, 79.9%). Kugelrohr distillation [67°C (0.020 mm)] afforded an analytical sample: mp 55-58°C; IR (CCl_4) 1725, 1480, 1265, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ9.73 (d, J = 3.0 Hz, 1H), 7.23 (t, J = 8.0 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 4.08 (m, 1H), 3.82 (s, 3H), 2.98 (m, 2H), 2.52 – 2.10 (m, 2H). Upon irradiation at δ4.08, the signal at δ9.73 collapsed to a singlet and the multiplet at δ2.52 – 2.10 was also simplified. Irradiation of the multiplet at δ2.52 – 2.10 resulted in simplification of both multiplets at δ4.08 and δ2.98. ^{13}C NMR ($CDCl_3$, 22.63 MHz) δ200.5, 156.5, 146.9, 129.6, 126.7, 117.3, 108.2, 55.8, 55.2, 32.2, 25.3; exact mass, m/z 176.0840 (calcd for $C_{11}H_{12}O_2$, m/z 176.0837). Anal. calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.74; H, 6.78.

2,3-Dihydro-7-methoxy-1H-indene-1-carboxylic acid (65)

Chromic acid[53] (ca. 0.5 mL; 2.7 M) was added dropwise to a cold (0°C) solution of aldehyde **69** (99.3 mg, 0.564 mmol) in acetone (5 mL), until an orange colouration persisted and starting material was no longer detectable (TLC, silica, 1:2 hexane – ethyl acetate). Water (ca. 10 mL) was added and the aqueous solution was extracted with ether (2 × ca. 20 mL). The combined ether layers were extracted with 5% aqueous sodium hydroxide (2 × ca. 20 mL). The basic aqueous layer was acidified to pH 1 with concentrated hydrochloric acid and then back-extrated with ether (2 × ca. 30 mL). The combined ether layers were washed with brine (1 × ca. 30 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) with 1:2 hexane – ethyl acetate, followed by 1:1 hexane – ethyl acetate gave **65** (97.8 mg, 90%): mp 142-143°C; FTIR (nujol) 1703.6, 1592.5, 1485.2, 1269.0, 1221.5, 1078.0 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz, 200 MHz) δ7.22 (t, J = 7.5 Hz, 1H), 6.90 (d, J = 7.0 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 4.10 (dd, J = 5.0, 7.5 Hz, 1H), 3.84 (s, 3H), 3.15 (m, 1H), 2.95 (ddd, J = 5.0, 7.5, 16 Hz, 1H), 2.43 (m, 2H). Upon irradiation at δ2.43 the signal at δ4.10 collapsed to a singlet and the signals at δ2.95 and δ3.15 collapsed to doublets, each with J = 16 Hz. ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ180.3 (s), 156.1 (s),

146.7 (s), 129.5 (d), 128.3 (s), 117.2 (d), 108.3 (d), 55.4 (q), 47.7 (d), 32.3 (t), 30.2 (t); exact mass, m/z 192.0785 (calcd for $C_{11}H_{12}O_3$, m/z 192.0786). Anal. calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.85; H, 6.26.

Methyl 2,3-dihydro-7-methoxy-1H-indene-1-carboxylate (**70**)

a) Anhydrous potassium carbonate (340 mg, 2.46 mmol) was added to a solution of acid **65** (431 mg, 2.24 mmol) and dimethyl sulfate (0.23 mL, 312 mg, 2.47 mmol) in acetone (6 mL). The mixture was stirred under reflux for 18 h, cooled to room temperature, and filtered. The solid was washed with acetone (3 × ca. 10 mL) and the combined filtrates were evaporated. The residue was kept under oil pump vacuum overnight to remove the excess of dimethyl sulfate. Flash chromatography of the residue over silica gel (3 × 15 cm) with 5:1 hexane – ethyl acetate gave **70** (440.4 mg, 95%). Kugelrohr distillation [83°C (0.400 mm)] provided an analytical sample: IR (CCl_4) 1735, 1480, 1265, 1165 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ7.19 (t, J = 7.5 Hz, 1H), 6.85 (d, J = 7.5 Hz, 1H), 6.67 (d, J = 8.0 Hz, 1H), 4.05 (dd, J = 5.5, 8.5 Hz, 1H), 3.78 (s, 3H), 3.68 (s, 3H), 3.11 (m, 1H), 2.91 (m, 1H), 2.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ175.2 (s), 156.2 (s), 146.4 (s), 129.1 (d), 129.0 (s), 116.9 (d), 108.2 (d), 55.3 (q), 51.6

(q), 47.8 (d), 32.3 (t), 30.4 (t); exact mass, m/z 206.0947 (calcd for $C_{12}H_{14}O_3$, m/z 206.0943). Anal. calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.79; H, 6.73.

b) Alternate procedure: Ethereal diazomethane solution was added dropwise, with stirring, to an ice-cold solution of acid **65** (40.0 mg, 0.208 mmol) in anhydrous diethyl ether (2.0 mL), until a yellow colouration persisted. The excess of reagent was destroyed by addition of a little silica gel and the mixture was filtered and evaporated. Kugelrohr distillation [83°C (0.400 mm)] gave **70** (42.6 mg, 99%).

Preparation and deuterium oxide quench of lithium 2,3-dihydro-1-lithio-7-methoxy-1H-indene-1-carboxylate (**71**)

a) Acid **65** (81.3 mg, 0.423 mmol) in THF (2.0 mL plus 1.0 mL rinse) was added dropwise over *ca.* 2 min to a cold (-78°C) solution of LDA [prepared from *n*-butyllithium (0.58 mL, 1.6 *M* in hexane, 0.93 mmol) and diisopropylamine (0.13 mL, 93.9 mg, 0.93 mmol) in THF (2.0 mL)] under argon. The mixture was stirred at -78°C for 15 min, at room temperature for 15 min, and at 50°C for 1 h.[54] The reaction mixture was quenched by addition of D_2O (*ca.* 0.5 mL). Dilute hydrochloric acid (*ca.* 10 mL, 1 *M*) was added and the aqueous layer was extracted with ether (2 × *ca.* 10

mL). The combined extracts were washed with dilute hydrochloric acid (1 × ca. 10 mL), water (1 × ca. 10 mL), and brine (1 × ca. 10 mL), dried, and evaporated to give **72**. These reaction conditions allowed complete deuterium incorporation at the position alpha to the carboxylic acid functionality, as shown by the ^1H NMR ($CDCl_3$, 80 MHz) of the crude residue: δ7.25 (t, J = 8.0 Hz, 1H), 6.90 (d, J = 7.0 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 3.8 (s, 3H), 3.05 (m, 2H), 2.43 (m, 2H).

b) The general procedure of reference 55 was used: n-butyllithium (0.43 mL, 1.55 M in hexane, 0.66 mmol) was added dropwise over ca. 3 min to a cold (0°C) solution of acid **65** (60.6 mg, 0.315 mmol) in THF (2.0 mL) under argon. The clear yellow solution was stirred at 0°C for 1 h and then quenched by addition of D_2O (0.5 mL). Stirring was continued at room temperature for 20 min. Dilute hydrochloric acid (ca. 5 mL, 1 M) was added and the mixture was extracted with ether (2 × 10 mL). The combined extracts were dried and evaporated, and the residue was kept under oil pump vacuum for 4 h. The ^1H NMR spectrum [($CDCl_3$, 200 MHz) δ7.22 (t, J = 7.5 Hz, 1H), 6.88 (d, J = 7.5 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 3.84 (s, 3H), 3.12 (m, 1H), 2.92 (m, 1H), 2.40 (m, 2H)] of the residue indicated 100% deuterium incorporation at the α-position of the carboxylic acid as judged by the absence

of a signal at δ4.10.

Preparation and deuterium oxide quench of methyl 2,3-dihydro-1-lithio-7-methoxy-1H-indene-1-carboxylate (**73**)

Ester **70** (131.0 mg, 0.6351 mmol) in THF (2.0 mL plus 1.6 mL rinse) was added dropwise over ca. 10 min to a cold (-78°C) solution of LDA [prepared from diisopropylamine (0.20 mL, 144 mg, 1.43 mmol) and n-butyllithium (0.56 mL, 1.7 M in hexane, 0.95 mmol) in THF (2.0 mL)] under argon. Aliquots of the reaction mixture were removed at intervals and quenched with D_2O. Saturated aqueous ammonium chloride (ca. 5 mL) was added and the aqueous layer was extracted with ether (2 × ca. 15 mL). The combined extracts were washed with brine (1 × ca. 15 mL), dried, and evaporated to give **74**. A 30 min reaction period at -78°C allowed the most efficient generation of the carbanion **73**: ^1H NMR ($CDCl_3$, 80 MHz) δ7.2 (t, J = 8.0 Hz, 1H), 6.9 (d, J = 7.0 Hz, 1H), 6.7 (d, J = 8.0 Hz, 1H), 3.8 (s, 3H), 3.7 (s, 3H), 3.05 (m, 2H), 2.4 (m, 2H).

Attempted acylation of carbanion **73** with phthalic anhydride

Ester **70** (16 mg, 0.079 mmol) in THF (0.5 mL plus 0.5 mL rinse) was added to a cold (-78°C) solution of LDA

[prepared from n-butyllithium (0.32 mL, 1.39 M in hexane, 0.445 mmol) and diisopropylamine (0.066 mL, 48 mg, 0.47 mmol) in THF (2.0 mL)] under argon and the mixture was stirred for 1.5 h. Phthalic anhydride (26 mg, 0.178 mmol) in THF (1.0 mL plus 0.5 mL rinse) was added and stirring was continued at -78°C for 30 min and then at 0°C for 30 min. The reaction was quenched by addition of saturated aqueous ammonium chloride (ca. 2 mL). Water (ca. 5 mL) was added and the mixture was extracted with ether (2 × ca. 15 mL). The combined extracts were washed with water (1 × ca. 10 mL), 5% aqueous sodium bicarbonate (1 × ca. 10 mL), and brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) with 1:1 hexane – ethyl acetate followed by ethyl acetate gave a small amount (3.9 mg) of an apparently homogeneous compound (TLC, silica, 1:1 hexane – ethyl acetate). The ^{1}H NMR ($CDCl_3$, 200 MHz) spectrum however, showed the residue to be a complex mixture of compounds.

Diethyl 3,6-dihydroxy-1,2-benzenedicarboxylate (78)

2,5-Bis(trimethylsiloxy)furan[56] (1.2 mL, 1.2 g, 4.91 mmol) was added to diethyl maleate (2.4 mL, 2.55 g, 14.83 mmol) under argon. The mixture was stirred at 60°C for 24 h and then cooled to room temperature. Tetrabutylammonium fluoride (8 mL, 1.0 M solution in THF, 8.0 mmol) and wet

acetonitrile (1:1 water – acetonitrile, 5 mL) were added and the mixture was stirred at room temperature overnight. Water (ca. 30 mL) was added and the aqueous layer was extracted with ether (1 × ca. 40 mL) and dichloromethane (1 × ca. 40 mL). The combined extracts were washed with brine (1 × ca. 30 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (4 × 15 cm) with 2:1 hexane – ethyl acetate gave **78** as a white solid (518.8 mg, 41%): mp 83-90°C; FTIR (CCl_4, cast) 3251.1, 1690.9, 1467.8, 1312.4, 1296.8, cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ8.60 (s, 2H), 7.10 (s, 2H), 4.36 (q, J = 7.0 Hz, 4H), 1.36 (t, J = 7.0 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ168.8, 151.9, 123.4, 113.3, 62.0, 13.9; exact mass, m/z 254.0793 (calcd for $C_{12}H_{14}O_6$, m/z 254.0790). Anal. calcd for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55. Found: C, 56.63; H, 5.54.

Diethyl 3,6-dimethoxy-1,2-benzenedicarboxylate (**79**)

Anhydrous potassium carbonate (510 mg, 3.69 mmol) was added to a solution of **78** (371.2 mg, 1.46 mmol) and dimethyl sulfate (0.35 mL, 466 mg, 3.70 mmol) in acetone (5 mL, reagent grade). The mixture was stirred at reflux for 18 h, cooled to room temperature, and filtered. The solid was washed with acetone (ca. 30 mL). The combined filtrates were evaporated and the residue was kept under

oil pump vacuum for *ca.* 24 h to remove the excess of dimethyl sulfate. Flash chromatography of the residue over silica gel (3 × 15 cm) with 3:1 hexane – ethyl acetate gave **79** (382 mg, 93%) as a white solid: mp 101-103°C; FTIR (CCl_4, cast) 1726.3, 1714.1, 1449.5, 1281.8, 1237.8, 1060.5 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ6.95 (s, 2H), 4.33 (q, J = 7.0 Hz, 4H), 3.82 (s, 6H), 1.34 (t, J = 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ165.7, 151.2, 123.5, 115.2, 61.5, 57.1, 14.1; exact mass, m/z 282.1106 (calcd for $C_{14}H_{18}O_6$, m/z 282.1103). Anal. calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.47; H, 6.38.

Attempted acylation of dianion **71** with diethyl 3,6-dimethoxy-1,2-benzenedicarboxylate (**79**)

Acid **65** (55.3 mg, 0.2875 mmol) in THF (2.0 mL plus 1.0 mL rinse) was added dropwise over *ca.* 2 min to a cold (-78°C) solution of LDA (0.70 mL, 1.0 *M* stock solution,* 0.70 mmol) under argon. The solution was stirred at -78°C for 30 min, at room temperature for 10 min, and then at 50°C for 1 h before being cooled to -78°C. Diester **79** (113.4 mg, 0.4017 mmol) in THF (2.0 mL) was injected

*Prepared from diisopropylamine (1.00 mL, 0.722 g, 7.13 mmol) and *n*-butyllithium (4.00 mL, 1.55 *M* in hexane, 6.20 mmol) and THF (1.2 mL).

quickly and the mixture was stirred at -78°C for 20 min, at 0°C for 30 min, and at room temperature for 1.5 h. Saturated aqueous ammonium chloride (6 mL) and ether (3 mL) were added and the mixture was stirred at room temperature overnight. Dilute hydrochloric acid (ca. 15 mL, 1 M) was added and the aqueous layer was extracted with ether (2 × ca. 15 mL). The combined extracts were washed with brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm) with 2:1 hexane – ethyl acetate, followed by 1:1 hexane – ethyl acetate allowed recovery of starting materials **79** (85.0 mg, 75%) and **65** (20.4 mg, 37% - as a slightly impure sample) as the major components of the reaction mixture.

2,5-Dimethoxybenzoyl chloride (**80**)

Oxalyl chloride (1.34 mL, 1.95 g, 15.4 mmol) was added to a cooled (0°C) solution of 2,5-dimethoxybenzoic acid (1.40 g, 7.68 mmol) in benzene (10 mL). The mixture was stirred at room temperature for 12 h and the solvent and excess of reagent were then evaporated. Kugelrohr distillation [95°C (0.5 mm)] of the residue provided **80** (1.47 g, 95%) as a low melting, yellow solid: mp 37-45°C; IR (CCl_4) 1780, 1490, 1278, 1230, 1160, 1048 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ7.59 (d, J = 3.0 Hz, 1H), 7.16 (dd, J =

3.1, 9.5 Hz, 1H), 6.95 (d, J = 9.0 Hz, 1H), 3.92 (s, 3H), 3.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 22.63 MHz) δ164, 154.1, 153.0, 122.5, 118.3, 113.7, 56.6, 56.0; low resolution mass spectrum: m/z 200 ($M^{+\cdot}$, 25.4% of base peak), 202 ($M^{+\cdot}$, 8.3% of base peak).

Methyl 2,3-dihydro-1-(2,5-dimethoxybenzoyl)-7-methoxy-1H-indene-1-carboxylate (**82**)

Ester **70** (220 mg, 1.07 mmol) in THF (2.0 mL plus 1.0 mL rinse) was added dropwise over 10 min to a cold (-78°C) solution of LDA [prepared from diisopropylamine (0.22 mL, 159 mg, 1.57 mmol) in THF (4.0 mL) and n-butyllithium (0.75 mL, 1.7 M in hexane, 1.28 mmol)] under argon. The mixture was stirred at -78°C for 30 min. Acid chloride **80** (535 mg, 2.67 mmol) in THF (2.0 mL plus 1.0 mL rinse) was injected quickly and stirring was continued at -78°C for 10 min and then at 0°C for 20 min. The reaction was quenched by addition of saturated aqueous ammonium chloride (ca. 10 mL). Water was added (ca. 30 mL) and the mixture was extracted with ether (2 × ca. 30 mL). The combined extracts were washed with water (ca. 20 mL), 5% aqueous sodium bicarbonate (ca. 20 mL) and brine (ca. 20 mL), dried, and evaporated. The residue was washed with a 1:1 hexane – ethyl acetate mixture (ca. 10 mL) and the supernatant was carefully removed to leave a white

solid. This solid was washed with ether (ca. 10 mL) and dried to give **82** (214 mg). The ether washings were chilled to facilitate crystallization and a second portion of **82** (107 mg) was collected (321 mg in all, 81%): mp 121-124°C; FTIR (CCl_4, cast) 1722.7, 1659.5, 1497.7, 1244.3, 1226.0, 1219.1, 1115.4, 1085.5, 1039.2, 1017.3, 995.1, 828.4, 774.3 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ7.28 (d, J = 3.1 Hz, 1H), 7.20 (t, J = 7.8 Hz, 1H), 6.97 (dd, J = 3.1, 8.9 Hz, 1H), 6.84 (dd, J = 0.5, 7.4 Hz, 1H), 6.76 (d, J = 8.9 Hz, 1H), 6.66 (d, J = 7.9 Hz, 1H), 3.78 (s, 3H), 3.68 (s, 3H), 3.65 (s), 3.64 (s), 3.00 (m, 2H), 2.88 (m, 1H), 2.65 (m, 1H). The signals at δ3.65 and 3.64 together have an area which corresponds to 6H. ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ199.1, 172.6, 156.6, 153.4, 151.2, 147.1, 130.0, 129.8, 129.0, 118.3, 116.9, 114.5, 111.8, 109.2, 71.1, 55.7, 55.4, 55.3, 51.7, 36.3, 31.5; exact mass, m/z 370.1415 (calcd for $C_{21}H_{22}O_6$, m/z 370.1417). Anal. calcd for $C_{21}H_{22}O_6$: C, 68.10; H, 6.00. Found: C, 67.83; H, 6.00.

Attempted preparation of 2,3-dihydro-7-methoxy-1H-indene-1-spiro-2'-(4',7'-dimethoxy-[2H]-inden-1',3'-dione) (**83**) from **82**:

a) 2,3-Dihydro-1-(2,5-dihydroxybenzoyl)-7-hydroxy-1H-indene (**84**). Aluminum chloride (164 mg, 1.23 mmol) was

added to a solution of β-ketoester **82** (114.2 mg, 0.308 mmol) in benzene (5.0 mL) and the mixture was stirred under reflux for 4 h until starting material was no longer detectable (TLC, silica, 2:1 hexane – ethyl acetate). Water (ca. 15 mL) was added and the mixture was extracted with ether (2 × ca. 15 mL). The combined extracts were washed with 5% aqueous sodium bicarbonate (ca. 10 mL) and brine (ca. 10 mL), dried, and evaporated. The ^{1}H NMR spectrum ($CDCl_3$, 80 MHz) of the residue showed at least one methoxy signal (δ 3.75) and signals at δ 11.4 and 11.8 which correspond to the chemical shifts expected for phenolic hydroxyls capable of intramolecular hydrogen bonding. The crude residue was further exposed to aluminum chloride (75 mg, 0.56 mmol) in refluxing benzene (5 mL) overnight. The reaction was worked up as previously described. Flash chromatography of the residue over silica gel (2 × 15 cm) with 3:2 hexane – ethyl acetate allowed separation of **84** (84 mg) as a slightly impure (TLC) sample: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 11.8 (s, 1H), 7.33 (d, J = 3 Hz, 1H), 7.10 (t, J = 8.0 Hz, 1H), 7.02 (dd, J = 3.0, 8.0 Hz, 1H), 6.86 (m, 2H), 6.58 (d, J = 8.0 Hz, 1H), 5.92 (s, 1H), 5.76 (s, 1H), 4.93 (dd, J = 6.0, 8.0 Hz, 1H), 3.00 (m, 2H), 2.56 (m, 1H), 2.20 (m, 1H); low resolution mass spectrum: m/z 270 ($M^{+\cdot}$, 30.4% of base peak).

b) Boron trifluoride etherate (0.041 mL, 50.7 mg, 0.445 mmol) was added to a cold (-20°C) suspension of **82** (55 mg, 0.148 mmol) in ether (3.0 mL) under argon. The reaction mixture was stirred at room temperature for 16 h. Water (ca. 10 mL) was added and the mixture was extracted with ether (2 × ca. 20 mL). The combined extracts were washed with brine (1 × ca. 10 mL), dried, and evaporated to leave a white solid (59 mg). Analysis of the crude material [(TLC, silica, 2:1 hexane – ethyl acetate) and ^{1}H NMR (80 MHz)] showed only the presence of starting material **82**.

c) Boron trifluoride etherate (0.05 mL, 62 mg, 0.544 mmol) was added to a solution of **82** (18 mg, 0.0486 mmol) in dioxane (2.0 mL) under argon. The mixture was stirred at 50°C for 48 h and then at 100°C for 24 h. Analysis of the reaction mixture (TLC, silica, 2:1 hexane – ethyl acetate) showed only the presence of starting material. The mixture was cooled to room temperature and worked up as described for the previous experiment. The IR spectrum of the crude residue served to identify the material as compound **82**.

d) Titanium tetrachloride (0.05 mL, 86 mg, 0.45 mmol) was added to a solution of **82** (18.7 mg, 0.0504 mmol) in benzene (1.0 mL) under argon. The brown solution was stirred at room temperature overnight. Analysis of the

reaction mixture (TLC, silica, 2:1 hexane – ethyl acetate) showed only the presence of starting material. The reaction was worked up as described for the previous experiments, and the identity of the product was confirmed by its ^{1}H NMR (80 MHz) spectrum.

e) p-Toluenesulfonic acid monohydrate (2 crystals) was added to a solution of **82** (20.8 mg, 0.0561 mmol) in benzene (1.5 mL) and the mixture was stirred at room temperature for 72 h. Analysis of the reaction mixture (TLC, silica, 2:1 hexane – ethyl acetate) showed only the presence of starting material. Additional benzene (2.0 mL) and p-toluenesulfonic acid (2 crystals) were added and stirring was continued at reflux for 48 h. The mixture was cooled to room temperature and water (ca. 5 mL) and ether (ca. 5 mL) were added. The aqueous layer was extracted with ether (2 × ca. 10 mL) and the combined extracts were washed with 5% aqueous sodium bicarbonate (1 × ca. 10 mL) and brine (1 × ca. 5 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) with 3:1 hexane – ethyl acetate allowed separation of the major component (R_f = 0.60, silica, 2:1 hexane – ethyl acetate). The IR spectrum of this compound showed no absorbance in the carbonyl region. A second compound (R_f = 0.49, silica, 2:1 hexane – ethyl acetate) was isolated and its IR spectrum showed

absorbances at 1765 and 1685 cm^{-1}. The material was not characterized but from the IR spectrum it was clearly neither starting material nor the desired product.

2,5-Dimethoxybenzaldehyde (**85**)

Pyridinium chlorochromate (3.00 g, 13.9 mmol) was added in small portions over *ca.* 15 min to a cold (0°C) solution of 2,5-dimethoxybenzyl alcohol (585 mg, 3.48 mmol) in dichloromethane (10 mL). The mixture was stirred at room temperature for 2 h and then poured into cold (0°C) 2:1 hexane – ethyl acetate (*ca.* 20 mL). The mixture was filtered through a column of Florisil (8 × 2.5 cm) and the filtrate was evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm) with 2:1 hexane – ethyl acetate gave **85** (517 mg, 89.5%) as a white solid: mp 48-50°C; IR (CCl_4) 1685, 1495, 1465, 1420, 1392, 1278, 1260, 1220, 1160, 1048, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ10.45 (s, 1H), 7.35 (d, J = 3.0 Hz, 1H), 7.16 (dd, J = 9.0, 3.0 Hz, 1H), 6.97 (d, J = 9.0 Hz, 1H), 3.92 (s, 3H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ189.3, 156.7, 153.7, 125.1, 123.2, 113.4, 110.7, 56.2, 55.8; exact mass, m/z 166.0631 (calcd for $C_9H_{10}O_3$, m/z 166.0631).

Methyl 2,3-dihydro-1-[hydroxy(2,5-dimethoxyphenyl)methyl]-7-methoxy-1H-indene-1-carboxylate (**86**)

Ester **70** (197 mg, 0.955 mmol) in THF (2.0 mL plus 2.0 mL rinse) was added dropwise over 10 min to a cold (-78°C) solution of LDA (2.71 mL, 0.42 M stock solution, 1.14 mmol) under argon. The mixture was stirred at -78°C for 30 min and then at -20°C for 5 min. Zinc chloride etherate[96] (0.78 mL, 0.69 M, 0.54 mmol) was added and stirring was continued for 15 min before a solution of 2,5-dimethoxybenzaldehyde (171 mg, 1.03 mmol) in THF (2.0 mL plus 1.0 mL rinse) was injected quickly. The mixture was stirred at 0°C for 1 h and then at room temperature for 40 min. It was then quenched by addition of saturated aqueous ammonium chloride (ca. 5 mL). Water was added and the mixture was extracted with dichloromethane (2 × ca. 20 mL). The combined extracts were washed with water (1 × ca. 10 mL) and brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm) with 5:1 hexane – ethyl acetate followed by 2:1 hexane – ethyl acetate, allowed separation of starting materials **70** (12.3 mg, 4.2% recovery) and **85** (3.3 mg, 2% recovery) from the desired product **86** [261 mg, 73% (78%*)]. The latter appears as two distinct compounds

*Corrected for recovered starting material.

(TLC, silica, 2:1 hexane – ethyl acetate) which are partially separable by flash chromatography: Low R_f isomer (0.22, silica, 2:1 hexane – ethyl acetate): mp 139-143°C; IR (CCl_4) 3580, 2950, 1722, 1490, 1475, 1465, 1432, 1300, 1255, 1215, 1170, 1160, 1085, 1050 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ7.23 (t, J = 7.5 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.74 (m, 3H), 6.15 (d, J = 2.5 Hz, 1H), 6.06 (d, J = 4.5 Hz, 1H), 4.17 (d, J = 4.5 Hz, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 3.38 (s, 3H), 2.53 (ddd, J = 1.0, 9.0, 15.0 Hz, 1H), 2.41 (ddd, J = 2.0, 8.0, 13.0 Hz, 1H), 2.25 (m, 1H), 1.69 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ176.7, 156.8, 153.0, 150.9, 148.7, 129.6, 129.5, 129.3, 117.5, 115.1, 113.3, 111.4, 109.0, 69.8, 64.4, 56.1, 55.9, 55.3, 52.3, 33.7, 31.2; exact mass, m/z 372.1563 (calcd for $C_{21}H_{24}O_6$, m/z 372.1573). Anal. calcd for $C_{21}H_{24}O_6$: C, 67.73; H, 6.50. Found: C, 67.77; H, 6.47. High R_f isomer (0.33, silica, 2:1 hexane – ethyl acetate): mp 128-133°C; FTIR (CCl_4) 3495, 1701.5, 1427.1, 1265.6, 1244.7, 1208.5, 1169.1, 1157.4, 1077.0, 1052.3, 1039.7, 1021.7, 998.8, 969.5, 946.0, 795.8, 786.7, 776.7 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ7.34 (d, J = 3.0 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 6.67 (m, 2H), 6.53 (d, J = 7.5 Hz, 1H), 6.38 (d, J = 8.5 Hz, 1H), 5.93 (s, br, 1H), 4.89 (d, J = 2.5 Hz, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 3.73 (s, 3H), 3.20 (s, 3H), 2.86 (ddd, J = 1.0, 8.0, 12.0 Hz, 1H),

2.64 (m, 1H), 2.28 (m, 1H), 2.06 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ178.8, 156.8, 153.4, 150.9, 146.7, 131.1, 129.1, 128.8, 116.5, 114.6, 113.5, 110.1, 107.4, 67.7, 63.1, 56.0, 55.3, 55.1, 52.2, 32.2, 30.7.

2,3-Dihydro-1-[hydroxy(2,5-dimethoxyphenyl)methyl]-7-methoxy-1H-indene-1-carboxylic acid (**87**)

An aqueous solution of potassium hydroxide (30 mg, in 2 mL of H_2O, 0.53 mmol) was added to β-hydroxyester **86** (70 mg, 0.188 mmol) and the mixture was stirred at reflux for 2 h. The solution was cooled to room temperature and aqueous 5% sodium hydroxide was added (ca. 10 mL). The aqueous solution was extracted with ether (2 × ca. 15 mL), acidified to pH 1 by addition of 1 M hydrochloric acid, and then back-extracted with ether (2 × ca. 15 mL). The combined extracts were washed with brine (ca. 10 mL), dried, and evaporated. The residue was recrystallized from ether to give **87** (17 mg, 25%) as a white solid: mp 190-205°C; IR (CCl_4) 3580, 2970, 2930, 2895, 2860, 2830, 1695, 1475, 1462, 1260, 1215, 1115, 1082, 1045 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ7.23 (t, J = 8.0 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.73 (m, 3H), 6.27 (s, br, 1H), 5.96 (s, 1H), 3.91 (s), 3.90 (s), 3.72 (s, 3H), 3.43 (s, 3H), 2.60 (m, 1H), 2.40 (m, 2H), 1.85 (m, 1H). The singlets at δ3.91 and 3.90 together have an area which corresponds to

4H. Low resolution mass spectrum: m/z 358 ($M^{+\cdot}$, 1.1% of base peak).

Treatment of **87** with diazomethane gave a compound whose spectra (IR, ^1H NMR, MS) proved to be identical with those of the lower R_f diastereoisomer of **86**.

Attempted methylation of hydroxyester **86**

Compound **86** (24.8 mg, 0.0665 mmol) in DMF (1.0 mL plus 0.5 mL rinse) was added to a cold (0°C) suspension of sodium hydride (4 mg, 0.15 mmol) in DMF (1.0 mL) under argon. The mixture was slowly warmed to room temperature over 1 h with stirring, and then cooled to 0°C. Methyl iodide (0.005 mL, 11.4 mg, 0.0803 mmol) in DMF (0.1 mL) was added and stirring was continued for 4 h before the reaction was quenched by addition of saturated aqueous ammonium chloride (ca. 2 mL). Water (ca. 10 mL) was added and the mixture was extracted with ether (1 × ca. 15 mL) and dichloromethane (1 × ca. 15 mL). The combined extracts were washed with water (1 × ca. 10 mL) and brine (1 × ca. 10 mL), dried, and evaporated. Analysis of the crude residue [TLC, silica, 2:1 hexane – ethyl acetate, and ^1H NMR ($CDCl_3$, 80 MHz)] showed the presence of retro-aldol products **70** and **85**.

(E)-2,3-Dihydro-7-methoxy-1-[3-(trimethylsilyl)-2-propenyl]-1H-indene-1-carboxylic acid (**91**)

Acid **65** (311.4 mg, 1.62 mmol) in THF (4.0 mL plus 2.0 mL rinse) was added dropwise over ca. 10 min to a cold (-78°C) solution of LDA [prepared from diisopropylamine (0.57 mL, 41.1 mg, 4.07 mmol) in THF (6.0 mL) and n-butyllithium (2.7 mL, 1.39 M in hexane, 3.75 mmol)] under argon. The solution was stirred at -78°C for 1 h, at room temperature for 20 min, and at 50°C for 1 h. It was then cooled to -78°C and the vinyl silane **90**[34] (410 mg, 2.12 mmol) in THF (3.0 mL plus 2.0 mL rinse) was injected quickly. Stirring was continued at -78°C for 1.5 h, the cooling bath was removed and, after 15 min the reaction was quenched by addition of saturated aqueous ammonium chloride (ca. 10 mL). Water (ca. 10 mL) was added and the mixture was extracted with ether (2 × ca. 30 mL). The combined extracts were washed with water (1 × ca. 20 mL) and brine (1 × ca. 20 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm) with 5:2 hexane – ethyl acetate followed by 1:1 hexane – ethyl acetate gave **91** (363.6 mg, 73%) as a white solid: mp 123-129°C; FTIR (CH_2Cl_2, cast) 1693.6, 1481.1, 1264.6, 1246.1, 835.8 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ7.21 (t, J = 7.5 Hz, 1H), 6.84 (dd, J = 1.0, 7.5 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 5.78 (dt, J = 18.0, 7.0 Hz, 1H), 5.62 (dt, J = 18.5, 1.0 Hz, 1H), 3.86 (s, 3H), 2.99 (ddd, J = 5.0,

9.0, 15.0 Hz, 1H), 2.92 – 2.76 (m, 3H), 2.56 (ddd, J = 6.5, 9.0, 13.0 Hz, 1H), 2.19 (ddd, J = 5.5, 9.0, 14.0 Hz, 1H), -0.03 (s, 9H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ182.0 (s), 156.2 (s), 146.4 (s), 142.7 (d), 134.0 (d), 131.6 (s), 129.5 (d), 117.2 (d), 108.8 (d), 57.6 (s), 55.3 (q), 42.7 (t), 35.9 (t), 31.9 (t), -1.27 (q); exact mass, m/z 304.1499 (calcd for $C_{17}H_{24}O_3Si$, m/z 304.1495). Anal. calcd for $C_{17}H_{24}O_3Si$: C, 67.06; H, 7.945. Found: C, 66.98; H, 7.93.

2,3-Dihydro-7-methoxy-1H-indene-1-spiro-1'-(3'-cyclopenten-2'-one) (**92**)

Thionyl chloride (0.44 mL, 71.8 mg, 6.03 mmol) was added to a solution of acid **91** (183.5 mg, 0.6026 mmol) in ether (10 mL) under argon, and the mixture was stirred at room temperature for 14 h. The solvent and excess of reagent were evaporated and the residue was dried under oil-pump vacuum for 18 h.

The crude acid chloride in dichloromethane (2.0 mL plus 1.0 mL rinse) was added to a cold (0°C) suspension of aluminum chloride[35,57] (194.3 mg, 1.457 mmol) in dichloromethane (7.0 mL) and the bright orange-red solution was stirred at 0°C for 30 min. The reaction mixture was poured onto ice and extracted with ether (2 × ca. 20 mL). The combined extracts were washed with water

(1 × ca. 20 mL) and brine (1 × ca. 20 mL), dried, and evaporated. Flash chromatography of the residue twice over silica gel (2 × 15 cm) with 3:1 hexane – ethyl acetate gave the spirocyclopentenone **92** (85.8 mg, 66.3%). Recrystallization from hexane – ethyl acetate provided an analytical sample: mp 93-96°C; FTIR (nujol) 1695.9, 1585.6, 1305.5, 1264.3, 1080.8, 787.8 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ7.71 (dt, J = 2.5, 6.0 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 6.86 (d, J = 7.5 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 6.31 (dt, J = 2.5, 6.0 Hz, 1H), 3.65 (s, 3H), 3.04 (m, 3H), 2.81 (dt, J = 18.5, 2.5 Hz, 1H), 2.41 (dt, J = 12.0, 8.5 Hz, 1H), 1.97 (m, 1H). Upon irradiation at δ2.81 the signals at δ3.04, 6.31, and 7.71 were simplified. Irradiation at δ2.41 resulted in simplification of the multiplets at δ1.97 and δ3.04. ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ212.6 (s), 161.6 (d), 155.4 (s), 146.9 (s), 132.8 (d), 129.1 (d), 121.3 (s), 117.0 (d), 108.7 (d), 57.8 (s), 55.2 (q), 44.0 (t), 39.4 (t), 31.8 (t); exact mass, m/z 214.0998 (calcd for $C_{14}H_{14}O_2$, m/z 214.0993). Anal. calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.33; H, 6.63.

2,3-Dihydro-7-methoxy-1-(2-propenyl)-1H-indene-1-carboxylic acid (**93**)

Acid **91** (62.2 mg, 0.2042 mmol) in dichloromethane

(2.0 mL plus 1.0 mL rinse) was added to a cooled (0°C) suspension of aluminum chloride (89.5 mg, 0.6712 mmol) in dichloromethane (4 mL) under argon. The mixture was stirred at 0°C for 2 h and then at room temperature for 18 h. Water (ca. 10 mL) was added cautiously and the aqueous layer was extracted with ether (2 × ca. 20 mL). The combined extracts were washed with water (1 × ca. 10 mL) and brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm) with 1:1 hexane – ethyl acetate followed by 1:2 hexane – ethyl acetate afforded the product **93** (37.9 mg, 80%): IR (CCl_4) 3100-2800, 1695, 1475, 1435, 1260, 1080, 815 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ7.20 (t, J = 8.0 Hz, 1H), 6.83 (d, J = 7.5 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 5.60 (m, 1H), 5.03 (d, J = 17.0 Hz), 4.96 (d, J = 10.0 Hz), 3.76 (s, 3H), 2.97 (m, 2H), 2.79 (m, 2H), 2.49 (ddd, J = 6.0, 9.0, 13.0 Hz, 1H), 2.20 (m, 1H). The signals at δ5.03 and δ4.96 together have an area which corresponds to 2H. Upon irrdiation at δ5.60 the signals at δ5.03, 4.96 and 2.79 were simplified. Low resolution mass spectrum: m/z 232 ($M^{+\cdot}$, 30.9% of base peak).

Methyl 2,3-dihydro-7-methoxy-1-(2-propenyl)-1H-indene-1-carboxylate (**94**)

Ethereal diazomethane solution was added dropwise to

an ice-cold solution of acid **93** (27.6 mg, 0.1180 mmol) in anhydrous ether (1 mL), until a yellow colouration persisted. The excess of reagent was destroyed by addition of a little silica gel and the mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) with 5:1 hexane – ethyl acetate afforded ester **94** (24.7 mg, 84%): IR (CCl_4) 2945, 1732, 1478, 1260, 1230, 1165, 1082, 915 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ7.20 (t, J =7.5 Hz, 1H), 6.84 (d, J = 7.5 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 5.62 (m, 1H), 5.04 (d, J = 17.0 Hz), 4.96 (d, J = 10.0 Hz), 3.77 (s, 3H), 3.65 (s, 3H), 2.96 (m, 2H), 2.79 (m, 2H), 2.40 (ddd, J = 7.0, 9.0, 13.0 Hz, 1H), 2.19 (ddd, J = 6.0, 7.5, 13.0 Hz, 1H). The signals at δ5.04 and δ4.96 together have an area which corresponds to 2H. Exact mass, m/z 246.1257 (calcd for $C_{15}H_{18}O_3$, m/z 246.1256).

Attempted preparation of 2,3-dihydro-7-methoxy-1H-indene-1-spiro-1'-(3'-cyclopenten-2'-one) (**92**) from **94**

The general procedure of reference 61 was used: ester **94** (18.2 mg, 0.0738 mmol) in 3.3:1 THF – HMPA (0.65 mL of mixed solvents and 0.5 mL rinse with neat THF) was added dropwise over *ca.* 2 min, to a cold (-78°C) solution of LDA (0.35 mL, 0.312 *M* stock solution, 0.109 mmol) under argon. The flask was removed from the bath and stirring

was continued at room temperature for 17 h. Saturated aqueous ammonium chloride (ca. 2 mL) and water (ca. 10 mL) were added and the aqueous layer was extracted with ether (2 × ca. 15 mL). The combined extracts were washed with aqueous copper sulfate (2 × ca. 10 mL), water (1 × ca. 10 mL), and brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) with 5:1 hexane – ethyl acetate allowed recovery of starting material as the only major component (8.8 mg, 48%).

(E)-3-(Trimethylsilyl)propenal (**96**)

Pyridinium chlorochromate (89.0 g, 0.413 mol) was added in portions over 20 min to a stirred, cold (0°C) solution of (E)-3-(trimethylsilyl)propenol[34] (13.45 g, 0.103 mol) in dichloromethane. The reaction mixture was warmed slowly to room temperature over 1.5 h. Hexane (ca. 200 mL) was added and the black mixture was filtered through a column (5 × 10 cm) of Florisil. Additional hexane (ca. 200 mL) was used to rinse the product from the flask and column. Those fractions containing aldehyde were combined and spinning band distillation (130°C, atmospheric pressure) allowed separation of the desired compound **96** (no yield obtained for this reaction): IR (film) 2960, 1690, 1252, 1085, 994, 865, 845 cm^{-1}; ^1H NMR

(400 MHz) δ9.83 (d, J = 8.0 Hz, 0.05H), 9.46 (d, J = 7.5 Hz, 0.95H), 7.16 (d, J = 18.0 Hz, 1H), 6.47 (dd, J = 18.5, 7.5 Hz, 0.95 H), 0.14 (s, 9H). The relative areas of the low field signals (δ9.46, δ9.83) indicated that the trans and cis isomers were present in a ratio of ca. 19:1. ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ194.3, 158.1, 144.2, -2.0; mass spectrum (CI), m/z 146 (M+18).

(E)-2,3-Dihydro-7-methoxy-1-[1-hydroxy-3-(trimethylsilyl)-2-propenyl]-1H-indene-1-carboxylic acid (**97**)

Acid **65** (86.6 mg, 0.4505 mmol) in THF (2.0 mL plus 1.0 mL rinse) was added dropwise over ca. 5 min to a cold (-78°C) solution of LDA [prepared from diisopropylamine (0.15 mL, 108 mg, 1.07 mmol) in THF (2.0 mL) and n-butyllithium (0.67 mL, 1.55 M in hexane, 1.04 mmol)] under argon. The bright yellow solution was stirred at -78°C for 1 h, at room temperature for 10 min, and then at 50°C for 1 h. It was then cooled to -78°C and aldehyde **96** (63.5 mg, 0.495 mmol) in THF (1.0 mL plus 1.0 mL rinse) was injected quickly. The mixture was stirred at -78°C for 30 min, and at room temperature for 30 min. Saturated aqueous ammonium chloride (ca. 4 mL) and water (ca. 10 mL) were added and the aqueous layer was extracted with ether (2 × ca. 15 mL). The combined extracts were washed with water (1 × ca. 10 mL) and brine (1 × ca. 10 mL), dried,

and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm) with 1:2 hexane – ethyl acetate gave β-hydroxyacid **97** (35.5 mg, 24.6%) as a viscous yellow oil: IR (CCl_4) 3550, 3080-2840, 1690, 1465, 1305, 1260, 1245, 1175, 1085 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) showed the presence of two diastereoisomers in a ratio of ca. 1.2:1; δ7.21 (m, 1.1H), 6.78 (m, 2.5H), 6.00 – 6.53 (m, 2.3H), 5.04 (d, J = 4.0 Hz, 0.62H), 4.67 (d, J = 4.0 Hz, 0.47H), 3.86 (s, 1.4H), 3.84 (s, 1.8H), 2.88 (m, 2.2H), 2.55 (m, 1.1H), 2.29 (m, 1.1H), -0.03 (s, 4.0H), -0.09 (s, 5.2H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ182.0 (s), 156.0 (s), 155.8 (s), 147.6 (s), 147.0 (s), 143.5 (d), 142.5 (d), 132.4 (d), 131.8 (d), 130.3 (s), 130.0 (d), 118.1 (d), 117.4 (d), 109.4 (d), 108.6 (d), 77.3 (d), 73.9 (d), 62.5 (s), 55.8 (q), 55.4 (q), 34.0 (t), 32.4 (t), 31.1 (t), 30.1 (t), -1.4 (q), -1.6 (q); exact mass, m/z 305.1217 [calcd for $C_{16}H_{21}O_4Si$ ($M-CH_3$), m/z 305.1209].

(E)-2,3-Dihydro-7-methoxy-1-[1-acetoxy-3-(trimethylsilyl)-2-propenyl]-1H-indene-1-carboxylic acid (**98**)

A solution of acetic anhydride (0.5 mL, 541 mg, 5.30 mmol) and β-hydroxyacid **97** (18.6 mg, 0.0580 mmol) in pyridine (1.0 mL) was stirred at room temperature for 18 h. Ether (ca. 20 mL) and dilute hydrochloric acid (ca. 20 mL, 1 M) were added and the aqueous layer was extracted

with ether (1 × ca. 20 mL). The combined extracts were washed with dilute hydrochloric acid (1 × ca. 10 mL, 1 M), 5% aqueous sodium bicarbonate (2 × ca. 10 mL), and brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) with 1:1 hexane – ethyl acetate followed by neat ethyl acetate gave **98** (16.5 mg, 78%) as a mixture of diastereoisomers from which only the lower R_f isomer (TLC, silica, 1:1 hexane – ethyl acetate, R_f = 0.16) was cleanly separated. It had: IR (CCl_4) 2955, 1750, 1705, 1478, 1268, 1230, 1085 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ7.26 (t, J = 8.0 Hz, 1H), 6.81 (d, J = 7.0 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 6.29 (d, J = 4.0 Hz, 1H), 5.70 (d, J = 18.0 Hz, 1H), 5.52 (dd, J = 18.0, 4.0 Hz, 1H), 3.82 (s, 3H), 3.05 (ddd, J = 6.0, 9.0, 15.0 Hz, 1H), 2.82 (ddd, J = 5.5, 9.0, 15.0 Hz, 1H), 2.50 (m, 2H), 2.09 (s, 3H), -0.16 (s, 9H); exact mass, m/z 191.0705 [calcd for $C_{11}H_{11}O_3$ ($M-C_8H_{15}O_2Si$), m/z 191.0719].

Attempted cyclization of (E)-2,3-dihydro-7-methoxy-1-[1-acetoxy-3-(trimethylsilyl)-2-propenyl]-1H-indene-1-carboxylic acid (**98**)

Thionyl chloride (0.043 mL, 70 mg, 0.59 mmol) was added to a solution of β-acetoxyacid **98** (21.3 mg, 0.0587 mmol) in ether (2.0 mL) under argon, and the mixture was

stirred at room temperature for 15 h. The solvent and excess of reagent were evaporated and the residue was dried under oil pump vacuum for 2 h.

The crude acid chloride in dichloromethane (1.0 mL plus 0.5 mL rinse) was added to a cold (0°C) suspension of aluminum chloride (2.43 mg, 0.182 mmol) in dichloromethane (2.0 mL). The yellow solution was stirred at 0°C for 1.5 h and then at room temperature overnight. Water (ca. 10 mL) was added and the mixture was extracted with ether (2 × ca. 15 mL). The combined extracts were washed with brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) with 2:1 hexane – ethyl acetate allowed the separation of various fractions. Analysis [IR and ^{1}H NMR ($CDCl_3$, 200 MHz)] of these fractions showed no significant amount of the desired spirocyclopentenone.

2,3-Dihydro-7-methoxy-1H-indene-1-spiro-1'-(5'-hydroxy-3'-cyclopenten-2'-one) (**99**)

Spirocyclopentenone **92** (23.7 mg, 0.1106 mmol) in dioxane (1.0 mL plus 0.5 mL rinse) was added to a suspension of selenium dioxide (63.3 mg, 0.570 mmol) in dioxane. The mixture was stirred under reflux for 48 h, cooled to room temperature, and filtered through a pad of Florisil to remove the black precipitate. The filtrate

was diluted with water (ca. 10 mL) and extracted with ether (2 × ca. 15 mL). The combined extracts were washed with water (1 × ca. 10 mL) and brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) with 3:1 hexane – ethyl acetate followed by 1:1 hexane – ethyl acetate allowed separation of starting material (5.3 mg, 22.4% recovery) from the oxidized product **99** (3.5 mg, 13.7%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ7.56 (m, 1H), 7.27 (t, J = 8.0 Hz, 1H), 6.93 (d, J = 7.5 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 6.40 (dd, J = 6.0, 1.8 Hz, 1H), 5.24 (m, 1H), 3.74 (s, 3H), 3.10 (m, 2H), 2.50 (m, 1H), 2.20 (m, 1H), 2.00 (d, J = 6 Hz, 1H). Upon D_2O exchange the signal at δ2.00 disappeared and the signal at δ5.24 collapsed to a broad singlet. Low resolution mass spectrum: m/z 230 ($M^{+\cdot}$, base peak).

2,3-Dihydro-7-methoxy-1H-indene-1-spiro-1'-(3',4'-epoxy-cyclopentan-2'-one) (**100**)

The general procedure of reference 62 was used: spirocyclopentenone **92** (12.9 mg, 0.0602 mmol) in absolute ethanol (1.0 mL plus 0.5 mL rinse) was added to sodium peroxide (103 mg, 1.32 mmol) and the red mixture was stirred at room temperature. Water (0.20 mL, 200 mg, 11.1 mmol) was added slowly over 1.5 h. Dilute hydrochloric

acid (*ca.* 15 mL, 1 *M*) was added and the mixture was extracted with dichloromethane (2 × *ca.* 15 mL). The combined extracts were washed with water (1 × *ca.* 10 mL), and brine (1 × *ca.* 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) gave **100** (4.8 mg, 34.7%) as a pale yellow solid: IR (CCl_4) 1752, 1478, 1262, 1082 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ7.20 (t, J = 7.5 Hz, 1H), 6.85 (dd, J = 1.0, 8.0 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 3.97 (dt, J = 2.5, 1.0 Hz, 1H), 3.76 (s, 3H), 3.56 (d, J = 2.5 Hz, 1H), 2.97 (m, 2H), 2.38 [m, containing s(br) at δ2.45, 3H], 2.10 (ddd, J = 4.5, 6.5, 11.0 Hz, 1H). Irradiation at δ3.97 caused the signal at δ3.56 to collapse to a singlet. Upon irradiation at δ2.97, the signals at δ3.38 and δ2.10 were simplified. Exact mass, m/z 230.0942 (calcd for $C_{14}H_{14}O_3$, m/z 230.0942).

Attempted deprotonation and deuteration of **92**

The general procedure of reference 64 was followed: spirocyclopentenone **92** (19.3 mg, 0.0901 mmol) in THF (1.0 mL plus 0.5 mL rinse) was added to a cold (-78°C) solution of LDA (0.25 mL, 0.43 *M* stock solution, 0.108 mmol) under argon. The bright yellow solution was stirred at -78°C for 30 min. Deuterium oxide (0.1 mL) was added, and the flask was removed from the cooling bath and allowed to

warm to room temperature. Saturated aqueous ammonium chloride (ca. 2 mL) and water (ca. 10 mL) were added and the mixture was extracted with ether (2 × ca. 15 mL). The combined extracts were washed with water (1 × ca. 10 mL) and brine (1 × ca. 10 mL), dried, and evaporated. Analysis [TLC (silica, 2:1 hexane – ethyl acetate), IR, and ^{1}H NMR ($CDCl_3$, 400 MHz)] of the crude residue showed the presence of at least three compounds with the major component being the non-deuterated starting material **92**.

Attempted Diels-Alder reaction of **92** and (E,E)-1,4-diacetoxybuta-1,3-diene (**103**)

a) The general procedure of reference 66 was used: a solution of spirocyclopentenone **92** (32.8 mg, 0.153 mmol) in toluene (0.5 mL plus 0.2 mL rinse) was added to aluminum chloride (17.1 mg, 0.128 mmol) at 10°C and the mixture was stirred at room temperature for 40 min. (E,E)-1,4-Diacetoxybutadiene **103** (88.3 mg, 0.519 mmol) in toluene (0.5 mL plus 1.0 mL rinse) was added and the mixture was stirred at 70°C for 19 h. The mixture was poured into ice-water (ca. 20 mL) and the flask was rinsed with acetone (ca. 4 mL). The mixture was extracted with

ether (2 × ca. 25 mL) and the combined extracts were washed with 5% aqueous sodium bicarbonate (1 × ca. 20 mL) and brine (1 × ca. 20 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) with 5:1 hexane – ethyl acetate followed by 2:1 hexane – ethyl acetate allowed recovery of starting material [identified by ^{1}H NMR ($CDCl_3$, 200 MHz)] **92**, (29.4 mg, 89%) as a slightly impure sample (contaminated with an unidentified product from decomposition of diene **103**). This was the only major component of the reaction mixture.

b) A solution of spirocyclopentenone **92** (15.0 mg, 0.070 mmol) and diene **103** (22.4 mg, 0.132 mmol) in toluene (1.0 mL) was stirred at 100°C under argon for 30 h. The solvent was evaporated and flash chromatography of the residue over silica gel (1 × 15 cm) with 2:3 hexane – ethyl acetate gave several mixed fractions. Analysis [TLC (silica, 1:2 hexane – ethyl acetate) and ^{1}H NMR ($CDCl_3$, 200 MHz)] of the fractions showed the major component to be unreacted starting material **92**.

c) Ethylaluminum dichloride (0.055 mL, 1.8 M in toluene, 0.099 mmol) was added to a cold (ca. 10°C) solution of spirocyclopentenone **92** (23.2 mg, 0.108 mmol) in toluene (0.3 mL) under argon. The solution was stirred at room temperature for 30 min[66] before diene **103** (67.1 mg, 0.394 mmol) in toluene (1.6 mL) was added and stirring

was continued at 100°C for 43 h. The solution was cooled to room temperature, water (ca. 10 mL) was added and the mixture was extracted with ether (3 × ca. 15 mL). The combined extracts were washed with 5% aqueous sodium bicarbonate (1 × ca. 10 mL), water (1 × ca. 10 mL), and brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) with 2:1 hexane – ethyl acetate allowed separation of two major components. These were shown [^{1}H NMR ($CDCl_3$, 200 MHz)] to be unreacted starting materials **103** (63.0 mg, 94% recovery) and **92** (14.8 mg, 64% recovery).

(E,E)-1,4-Bis[(tert-butyldimethylsilyl)oxy]buta-1,3-diene (**104**)

The general procedure of reference 67 was followed using diacetate **103** (341.7 mg, 2.001 mmol) and methyllithium (6.4 mL, 1.56 M in diethyl ether, 10.0 mmol) in THF (4.0 mL), and tert-butyldimethylchlorosilane (1.52 g, 10.1 mmol) in THF (5.0 mL). A different work up was used though: water (ca. 10 mL) was added and the mixture was extracted with ether (2 × ca. 15 mL). The combined extracts were dried and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm) with 9:1 hexane – ethyl acetate gave (E,E)-1,4-bis[(tert-butyldimethylsilyl)oxy]buta-1,3-diene (494.6 mg, 78%) as a pale yellow

oil at room temperature (solidified upon refrigeration).

Attempted Diels-Alder reactions of **92** and (E,E)-1,4-Bis[(tert-butyldimethylsilyl)oxy]buta-1,3-diene (**104**)

a) A solution of spirocyclopentenone **92** (19.7 mg, 0.0919 mmol) and diene **104** (64.8 mg, 0.206 mmol) in toluene (1.0 mL) was stirred at 100°C under argon for 67 h. The mixture was cooled to room temperature, diluted with ether (ca. 15 mL) and washed with brine (1 × ca. 5 mL). The organic extract was dried and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm) with 5:1 hexane – ethyl acetate allowed separation of starting materials [identified by ^{1}H NMR ($CDCl_3$, 200 MHz)] **104** (37.5 mg as an impure sample contaminated with decomposition products) and **92** (18.0 mg, 91% recovery).

b) A mixture of spirocyclopentenone **92** (11.7 mg, 0.0546 mmol) and diene **104** (78.1 mg, 0.248 mmol) was stirred under argon at 130°C for 21 h and at 180°C for 24 h, and then cooled to room temperature. Flash chromatography of the reaction mixture over silica gel (2 × 15 cm) with 5:1 hexane – ethyl acetate allowed separation of the unreacted starting materials [identified by ^{1}H NMR ($CDCl_3$, 200 MHz)] **104** (60 mg as an impure sample contaminated with decomposition products) and **92** (10.6 mg, 90% recovery).

Methyl 1-(3-chloro-1-oxopropyl)-2,3-dihydro-7-methoxy-1H-indene-1-carboxylate (**105**)

Ester **70** (155.7 mg, 0.7549 mmol) in THF (1.0 mL plus 0.5 mL rinse) was added dropwise over ca. 5 min to a cold (-78°C) solution of LDA [prepared from diisopropylamine (0.16 mL, 115 mg, 1.14 mmol) in THF (3.0 mL) and n-butyllithium (0.75 mL, 1.4 M in hexane, 1.06 mmol)] under argon. The pale yellow solution was stirred at -78°C for 60 min before addition of 3-chloropropionyl chloride (0.18 mL, 240 mg, 1.89 mmol). The reaction mixture was stirred at -78°C for 30 min, at 0°C for 15 min, and at room temperature for 20 min, and was then quenched by addition of saturated aqueous ammonium chloride (ca. 5 mL). Water (ca. 5 mL) was added and the mixture was extracted with ether (2 × ca. 20 mL). The combined extracts were washed with water (1 × ca. 10 mL), 5% aqueous sodium bicarbonate (1 × ca. 10 mL), and brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (3 × 17 cm) with 5:1 hexane – ethyl acetate gave ester **70** (48.2 mg, 31% recovery) and β-ketoester **105** [88.6 mg, 39.6% yield (57.3% corrected for recovered starting material)]: IR (CCl_4) 1732, 1712, 1478, 1265, 1235 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ7.29 (t, J = 8.0 Hz, 1H), 6.90 (dd, J = 7.0, 1.0 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 3.89 (s, 3H), 3.77 (s, 3H), 3.73 (t, J = 6.5 Hz, 2H), 3.27 (dt, J = 17, 6.5 Hz, 1H), 3.00 (m, 3H), 2.88 (m, 1H), 2.53 (m,

1H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ202.6, 172.5, 156.2, 147.2, 130.6, 128.2, 117.7, 109.6, 105.09,* 105.05,* 69.9, 55.6, 52.5, 41.9, 38.9, 35.4, 31.7; exact mass, m/z 296.0826 (calcd for $C_{15}H_{17}O_4Cl$, m/z 296.0816).

Methyl 2,3-dihydro-1-(3-ethoxy-1-oxopropyl)-7-methoxy-1H-indene-1-carboxylate (**106**)

β-Ketoester **105** (26.5 mg, 0.0892 mmol), ethylene glycol (0.15 mL, 166 mg, 2.68 mmol), triethyl orthoformate (0.15 mL, 132 mg, 0.892 mmol), and p-toluenesulfonic acid monohydrate (one crystal) were stirred at 100°C in a small (ca. 2 mL capacity) flask with a sealed-on reflux condenser for 24 h. The mixture was cooled to room temperature and flash chromatography of the solution over silica gel (2 × 15 cm) with 5:1 hexane – ethyl acetate gave **105** (7.6 mg, 28.7% recovery of starting material) and ether **106** (4.0 mg, 14.6%). **106**: IR (CCl_4) 1735, 1710, 1478, 1268, 1235, 1130, 1105, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ7.25 (t, J = 7.5 Hz, 1H), 6.89 (d, J = 7.0 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 3.85 (s, 3H), 3.73 (s, 3H), 3.64 (t, J = 6.7 Hz, 2H), 3.43 (q, J = 6.7 Hz, 2H), 2.90 (m, 5H), 2.54 (m, 1H), 1.13 (t, J = 7.0 Hz, 3H); low

*These carbon signals may be noise artefacts.

resolution mass spectrum: m/z 306 ($M^{+\cdot}$, 6.5% of base peak).

Methyl 2,3-dihydro-7-methoxy-1-[3-(phenylthio)-1-oxopropyl]-1H-indene-1-carboxylate (**109**)

A stock solution of lithium thiophenoxide was prepared by addition of n-butyllithium (0.25 mL, 1.6 M in hexane, 0.40 mmol) to a cold (-78°C) solution of thiophenol (0.043 mL, 46.5 mg, 0.422 mmol) in THF (2.0 mL) under argon. The flask was removed from the cooling bath and stirring was continued for 0.5 h. A portion of this solution (0.5 mL, 0.18 mM, 0.090 mmol lithium thiophenoxide) was added to a cold (-78°C) solution of **105** (24.5 mg, 0.0825 mmol) in THF (1.0 mL). The mixture was stirred at -78°C for 10 min and then at room temperature for 3 h. It was then quenched with saturated aqueous ammonium chloride (ca. 5 mL). Water (ca. 5 mL) was added and the mixture was extracted with ether (2 × ca. 15 mL). The combined extracts were washed with water (1 × ca. 10 mL), and brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) with 5:1 hexane – ethyl acetate gave **105** (1.3 mg, 5.2% recovery of starting material) and **109** (14.2 mg, 46.5% yield). **109**: IR (CCl_4) 1730, 1710, 1478, 1438, 1432, 1298, 1265, 1230, 1082 cm^{-1}; ^1H NMR

($CDCl_3$, 400 MHz) δ7.38 (m, 5H), 7.16 (m, 1H), 6.85 (d, J = 7.0 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 3.73 (s, 6H), 3.11 (m, 3H), 2.91 (m, 2H), 2.80 (m, 2H), 2.48 (m, 1H): exact mass, m/z 370.1237 (calcd for $C_{21}H_{22}O_4S$, m/z 370.1239).

Methyl 2,3-dihydro-7-methoxy-1-[3-(4-methylphenyl-sulfonyl)-1-oxopropyl]-1H-indene-1-carboxylate (**110**)

A solution of **105** (43.1 mg, 0.1452 mmol) and sodium p-toluenesulfinate dihydrate (89.8 mg, 0.4191 mmol) in DMF (4.0 mL) was stirred at room temperature for 48 h. Water (ca. 10 mL) was added and the mixture extracted with ether (2 × ca. 20 mL). The combined ether extracts were washed with water (1 × ca. 10 mL) and brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm) with 2:1 hexane – ethyl acetate gave **110** (56.1 mg, 92.5%) as an oil: FTIR (CCl_4, cast) 1716.0, 1478, 1315.9, 1302.8, 1269.7, 1235, 1150.0, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ7.69 (d, J = 8.0 Hz, 1H), 7.30 (m, 3H), 6.87 (d, J = 7.5 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 3.86 (s, 3H), 3.73 (s, 3H), 3.33 (m, 2H), 3.26 (m, 1H), 2.99 (m, 1H), 2.85 (m, 3H), 2.50 – 2.41 (m, 4H; singlet at δ2.45). Upon irradiation at δ2.50 – 2.41 the multiplet at δ2.85 was simplified. ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ201.9, 172.3, 156.0, 147.1, 144.6, 136.2, 130.7, 129.8, 127.94, 127.85, 117.7, 109.6, 69.7,

55.6, 52.5, 51.4, 35.6, 32.1, 31.6, 21.6; exact mass, m/z 416.1302 (calcd for $C_{22}H_{24}O_6S$, m/z 416.1294).

Methyl 2,3-dihydro-7-methoxy-1-[1-hydroxy-3-(4-methylphenylsulfonyl)propyl]-1H-indene-1-carboxylate (**111**) and methyl 2,3-dihydro-7-methoxy-1-(1-oxopropyl)-1H-indene-1-carboxylate (**112**)

Sodium borohydride (15 mg, 0.40 mmol) was added in small portions to a cold (0°C) solution of β-ketoester **110** (46.6 mg, 0.112 mmol) in absolute ethanol (2.3 mL), over ca. 10 min. The mixture was stirred at 0°C for an additional 35 min and was then quenched with saturated aqueous ammonium chloride (ca. 2 mL). Water (ca. 5 mL) was added and the aqueous solution was extracted with ether (2 × ca. 20 mL). The combined extracts were washed with water (1 × ca. 10 mL) and brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) with 5:1 hexane – ethyl acetate gave two products. The major product was alcohol **111** (33.4 mg, 71.4%), present as a mixture [ca. 5:1 (^{1}H NMR)] of diastereoisomers. Recrystallization of **111** from ethyl acetate provided an analytical sample: mp 140-143°C; FTIR (nujol) 3520, 1720, 1590, 1280, 1265, 1150, 1080, 1060, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ7.71 (d, J = 8.0 Hz, 1.67H), 7.63 (d, J = 8.0 Hz, 0.32H), 7.28

(m, 3.53H), 6.89 (dd, J = 0.5, 7.5 Hz), 6.85 (d, J = 8.0 Hz), 6.74 (d, J = 8.0 Hz, 0.88H), 6.66 (d, J = 8.5 Hz, 0.19H), 4.70 (m, 0.19H), 3.91 (m, 0.82H), 3.80 (s, 2.46H), 3.74 (s, 0.41H), 3.67 (s, 2.46H), 3.63 (s, 0.57H), 3.51 (d, J = 9.0 Hz, 0.94H), 3.40 (m, 1.04H), 3.15 (m, 0.88H), 2.94 (t, J = 7 Hz, 1.89H), 2.46 – 2.31 (m, singlet at δ2.44, 4.79H), 1.91 (m, 0.88H), 1.76 (m, 1.04H). The signals at δ6.89 and δ6.85 together have an area which corresponds to 1.04H. Upon D_2O exchange the doublet at δ3.51 disappeared and the multiplet at δ3.91 was simplified. ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ178.0, 175.4, 156.0, 147.1, 146.6, 144.35, 144.26, 136.7, 129.9, 129.8, 129.7, 128.9, 128.0, 118.0, 117.5, 109.4, 108.7, 105.1, 73.0, 71.1, 63.8, 62.5, 55.6, 55.3, 54.0, 53.9, 52.2, 52.0, 34.3, 32.1, 30.9, 29.9, 25.7, 24.2, 21.6, 21.0;* mass spectrum (CI), m/z 436 (M+18). Anal. calcd for $C_{22}H_{26}O_6S$: C, 63.14; H, 6.26; S, 7.66. Found: C, 62.86; H, 6.38; S, 7.69. The minor reaction product was β-ketoester **112** (3.5 mg, 11.9%): FTIR (CCl_4, cast) 1731.0, 1711.9, 1590.1, 1480.4, 1297.8, 1269.2, 1234.5, 1080.7, 1068.8 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ7.25 (t, J = 7.5 Hz, 1H), 6.88 (d, J = 7.5 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H),

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*Not all of the signals of both diastereoisomers were resolved in this spectrum.

3.86 (s, 3H), 3.76 (s, 3H), 2.93 (m, 2H), 2.75 (m, 2H), 2.48 (m, 2H), 1.02 (t, J = 7.0 Hz, 3H); exact mass, m/z 262.1207 (calcd for $C_{15}H_{18}O_4$, m/z 262.1205).

3-(4-Methylphenylsulfonyl)propanal diethyl acetal (**113**)

A solution of 3-chloropropionaldehyde diethyl acetal (1.8 mL, 1.791 g, 10.73 mmol) and sodium p-toluenesulfinate dihydrate (3.00 g, 14.0 mmol) in DMF (16 mL) was stirred under reflux for 24 h. The reaction mixture was cooled to room temperature, diluted with water (ca. 30 mL) and extracted with ether (2 × ca. 30 mL). The combined extracts were washed with water (1 × ca. 20 mL) and brine (1 × ca. 20 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (5 × 15 cm) with 3:1 hexane – ethyl acetate gave **113** (1.128 g, 36.7%) as a pale yellow oil: IR (film) 2980, 2930, 2895, 2880, 1375, 1315, 1302, 1290, 1148, 1125, 1090, 1065, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ7.80 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 4.54 (t, J = 5.0 Hz, 1H), 3.60 (m, 2H), 3.45 (m, 2H), 3.17 (m, 2H), 2.47 (s, 3H), 1.99 (m, 2H), 1.17 (t, J = 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ144.6, 136.2, 129.8, 128.0, 100.7, 62.0, 51.8, 27.3, 21.5, 15.1; exact mass, m/z 286.1235 (calcd for $C_{14}H_{22}O_4S$, m/z 286.1239).

3-(4-Methylphenylsulfonyl)propanal (**114**)

The general procedure of reference 93 was used: an aqueous solution of oxalic acid (10% w/v, 1 mL) was added to a stirred suspension of silica gel 60 (70-230 mesh, 3.0 g) in dichloromethane (14 mL). Once the aqueous droplets had been adsorbed onto the silica (ca. 5 min), diethyl acetal **113** (615.2 mg, 2.148 mmol) in dichloromethane (2.0 mL plus 1.0 mL rinse) was added and the reaction mixture was stirred at room temperature for 48 h.

Sodium bicarbonate (ca. 0.5 g) was added and the mixture was stirred for 5 min. The solids were filtered off and the filtrate was evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm) first with 2:1 hexane – ethyl acetate and then with 1:1 hexane – ethyl acetate, allowed separation of unreacted starting material **113** (170.1 mg, 27.6% recovery) from aldehyde **114** (220.3 mg, 48.3%), which had: IR (film) 1720, 1695, 1410, 1318, 1302, 1290, 1232, 1145, 1085, 828, 818 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ9.72 (s, 1H), 7.78 (d, J = 7.9 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 3.40 (t, J = 7.5 Hz, 2H), 2.93 (t, J = 7.5 Hz, 2H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ197.0, 145.0, 135.6, 130.0, 127.9, 49.1, 36.5, 21.5; exact mass, m/z 212.0509 (calcd for $C_{10}H_{12}O_3S$, m/z 212.0507).

Methyl 2,3-dihydro-7-methoxy-1-[1-hydroxy-3-(4-methylphenylsulfonyl)propyl]-1H-indene-1-carboxylate (**111**) from **70** and **114**

Ester **70** (125.0 mg, 0.606 mmol) in THF (2.0 mL plus 1.0 mL rinse) was added dropwise over ca. 10 min to a cold (-78°C) solution of LDA [1.5 mL, 0.60 M stock solution, 0.91 mmol, prepared hexane, 6.0 mmol] under argon. The solution was stirred at -78°C for 50 min and then aldehyde **114** (227.1 mg, 1.07 mmol) in THF (2.0 mL plus 1.0 mL rinse) was added rapidly. Stirring was continued at -78°C for 30 min and then at room temperature for 15 min. The mixture was quenched with saturated aqueous ammonium chloride (ca. 5 mL). Water (ca. 5 mL) was added and the aqueous layer was extracted with ether (2 × ca. 15 mL). The combined extracts were washed with water (1 × ca. 10 mL) and brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm) with 2:1 hexane – ethyl acetate gave **111** (198.3 mg, 78.2%). The material was identical with that made by sodium borohydride reduction of **110**, with the exception of the ratio of isomers. ^{1}H NMR showed the presence of two diastereoisomers in a ratio of ca. 1:1 as opposed to the ca. 5:1 ratio obtained from **110**.

Methyl 2,3-dihydro-7-methoxy-1-[3-(4-methylphenyl-sulfonyl)-1-[(trimethylsilyl)oxy]propyl]-1H-indene-1-carboxylate (115)

TRI-SIL[71] [(1:1 hexamethyldisilazane – chlorotrimethylsilane) from HMDS (0.2 mL, 0.78 mmol), TMCS (0.2 mL, 0.49 mmol)] was added to a solution of β-hydroxyester **111** (60.0 mg, 0.145 mmol) in DMSO (1.5 mL) at room temperature under argon, and the mixture was stirred for 3 h. Water (ca. 10 mL) was added and the aqueous solution was extracted with ether (2 × ca. 20 mL). The combined ether extracts were washed with dilute hydrochloric acid (1 × ca. 2 mL, 1 M), 5% aqueous sodium bicarbonate (1 × ca. 10 mL) and brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm) with 2:1 hexane – ethyl acetate gave silyl ether **115** (66.1 mg, 93%) as a mixture [ca. 3.5:1 (^{1}H NMR)] of diastereoisomers. Recrystallization from hexane – ethyl acetate provided an analytical sample: mp 145-148°C; FTIR (CCl_4, cast) 1728.9, 1479.1, 1317.0, 1254.0, 1250.0, 1150.6, 1140.2, 1101.8, 1085.7, 1065.3, 841.2 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (d, J = 8.0 Hz, 1.61H), 7.63 (d, J = 8.0 Hz, 0.56H), 7.37 (d, J = 8.0 Hz, 1.61H), 7.28 (d, J = 8.0 Hz, 0.25H), 7.17 (m, 1.01H), 6.80 (m, 1.05H), 6.62 (d, J = 8.0 Hz, 0.74H), 6.55 (d, J = 8.0 Hz, 0.25H), 5.00 (dd, J = 9.0, 3.5 Hz, 0.27H), 4.71 (dd, J = 8.5, 2.5 Hz,

0.74H), 3.73 (s, 2.35H), 3.62 (s, 0.68H), 3.57 (s, 0.68H), 3.54 (s, 2.35H), 3.25 – 3.06 (m, 1.85H), 3.06 – 2.84 (m, 2.10H), 2.45 (s, 1.98H), 2.44 (s, 0.99H), 2.35 (m, 1.85H), 2.21 (m, 0.99H), 1.82 (m, 0.74H), 1.51 (m, 0.43H), 0.076 (s, 2.13H), -0.325 (s, 6.80H). Irradiation at δ2.35 collapsed the multiplet at δ3.06 – 2.84 to a broad singlet. Irradiation at δ4.71 resulted in simplification of the multiplet at δ2.21. ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ174.7, 156.5, 147.9, 144.4, 136.5, 130.6, 129.8, 129.7, 129.5, 128.1, 128.0, 117.6, 117.3, 108.7, 108.4, 72.8, 72.5, 64.1, 55.2, 54.9, 54.7, 54.6, 51.8, 51.7, 32.4, 31.8, 30.4, 29.8, 28.4, 26.8, 26.1, 0.62, 0.020;* mass spectrum (CI), m/z 508 (M+18). Anal. calcd for $C_{25}H_{34}O_6SiS$: C, 61.19; H, 6.98; S, 6.53. Found: C, 61.22; H, 6.98; S, 6.60.

2,3-Dihydro-7-methoxy-1H-indene-1-spiro-1'-[3'-(4-methylphenylsulfonyl)-5'-(trimethylsilyl)oxy]-cyclopentan-2'-one (116)

The general procedure of reference 68 was used: ester sulfone **115** (130.2 mg, 0.2653 mmol) in THF (2.0 mL plus 1.0 mL rinse) was added dropwise over ca. 2 min to a

*Not all carbon signals of both diastereoisomers were resolved in this spectrum.

cold (-78°C) solution of LDA (1.1 mL, 0.60 M stock solution, 0.66 mmol) under argon. The bright yellow reaction mixture was stirred at -78°C for 1 h and then at 0°C for 1 h. It was then quenched with saturated aqueous ammonium chloride (ca. 5 mL). Water (ca. 5 mL) was added and the mixture was extracted with ether (2 × ca. 20 mL). The combined ether extracts were washed with water (1 × ca. 10 mL) and brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm) with 3:1 hexane – ethyl acetate gave compound **116** as a mixture [ca. 15.5:3.2:2.9:1 (^{1}H NMR)] of diastereoisomers (104 mg, 85%): mp 47-55°C; FTIR (CCl_4, cast) 1750.4, 1480, 1315, 1264.2, 1251.6, 1149.9, 1128.6, 1084.2, 879.4, 843.2, 775, 574.5 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ7.82 (m, 1.88 H), 7.36 (m, 1.88H), 7.16 (m, 1.00H), 6.78 (dd, J = 0.5, 7.5 Hz, 0.87H), 6.69 (d, J = 8.0 Hz, 0.13H), 6.60 [m, 0.80H; containing a doublet at δ6.61 (J = 8.5 Hz)], 5.01 (dd, J = 9.0, 7.0 Hz, 0.13H), 4.59 (dd, J = 10.5, 6.5 Hz, 0.70H), 4.45 (t, J = 9.0 Hz, 0.16H), 4.33 (m, 0.13H), 4.21 (m, 0.13H), 4.10 [m, 0.94H; contains a doublet of doublets at δ4.13 (J = 12.5, 7.75 Hz)], 3.86 (s, 0.38H), 3.68 (s, 2.01H), 3.60 (s, 0.43H), 3.46 (s, 0.13H), 2.86 (m, 2.12H), 2.59 (m, 0.87H), 2.42 (m, 4.29H; singlet at δ2.45), 2.34 – 2.15 (m, 0.67H; singlet at δ2.28), 2.05 (s, 0.27H), 1.92 (m, 0.16 H), 1.75

(m, 0.80 H), 1.28 (m, 0.54H), -0.2 (s, 0.54H), -0.3 (s, 0.80H), -0.4 (s, 7.2H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ207.9, 206.0, 156.3, 155.1, 148.0, 147.9, 146.9, 145.1, 145.0, 135.4, 130.0, 129.83, 129.79, 129.64, 129.61, 129.5, 129.4, 129.2, 117.2, 116.8, 116.7, 108.8, 108.7, 108.5, 74.7, 73.5, 72.4, 69.4, 69.0, 67.3, 67.1, 55.3, 55.2, 54.9, 37.8, 32.9, 32.5, 32.1, 31.9, 31.68, 31.65, 31.1, 29.2, 21.7, -0.28, -0.45, -0.59, -0.63;* mass spectrum (CI) m/z, 476 (M+18).

2,3-Dihydro-7-methoxy-1H-indene-1-spiro-1'-cyclopent-3'-en-2',5'-dione (**89**)

Chromic acid[53] (0.6 mL, 2.7 M, 1.6 mmol) was added dropwise to a cold (0°C) solution of **116** (80.8 mg, 0.176 mmol) in acetone (5 mL). The reaction mixture was stirred at 0°C for 30 min and then at room temperature for 75 min. Water (ca. 10 mL) was added and the aqueous solution was extracted with ether (2 × ca. 20 mL). The combined ether extracts were washed with water (1 × ca. 10 mL), 5% aqueous sodium bicarbonate solution (1 × ca. 10 mL) and brine (1 × ca. 10 mL), dried, and evaporated. The residue was loaded onto a column of silica gel (2 × 15 cm) and

*Not all of the carbon signals of the four diastereoisomers were resolved in this spectrum.

allowed to stand for ca. 10 min. Flash chromatography with 2:1 hexane – ethyl acetate then gave **89** (35.6 mg, 88.5%): mp 103.5-105°C; FTIR (CCl_4, cast) 2858, 1700.5, 1260, 1077.0 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ7.33 (s, 2H), 7.22 (t, J = 7.75 Hz, 1H), 6.91 (dd, J = 1.0, 7.5 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 3.62 (s, 3H), 3.19 (t, J = 7.5 Hz, 2H), 2.34 (t, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ206.0, 155.2, 148.3, 148.0, 130.4, 127.7, 117.5, 108.6, 61.3, 55.3, 34.2, 32.2; exact mass, m/z 228.0790 (calcd for $C_{14}H_{12}O_3$, m/z 228.0787). Anal. calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.71; H, 5.21.

2,3-Dihydro-7-methoxy-1H-indene-1-spiro-2'-[2H]-inden-1',3'-dione (**118**)

Diene **104** (32.6 mg, 0.1036 mmol) and enedione **89** (13.5 mg, 0.0591 mmol) were stirred at 140°C, under an argon atmosphere for 16 h. The reaction mixture was cooled to room temperature and flash chromatography of the residue over silica gel (1 × 15 cm) with 2:1 hexane – ethyl acetate gave **89** (7.8 mg, 57.8% recovery of starting material) and **118** (1.5 mg, 9.1% yield): FTIR (CCl_4, cast) 1740, 1705.3, 1590 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ8.03*

*The signals at δ8.03 and δ7.88 show the characteristic pattern of an AA'BB' system.

(m, 2H), 7.88 (m, 2H), 7.23 (t, J = 8.0 Hz, 1H), 6.94 (dd, J = 7.5, 0.75 Hz, 1H), 6.57 (d, J = 8.0 Hz, 1H), 3.42 (s, 3H), 3.28 (t, J = 7.25 Hz, 2H), 2.46 (t, J = 7.25 Hz, 2H); exact mass, m/z 278.0938 (calcd for $C_{18}H_{14}O_3$, m/z 278.0942).

2,3-Dihydro-7-methoxy-1H-indene-1-spiro-2'-[4',7'-bis-(tert-butyldimethylsilyl)oxy-3a',4',7',7a'-tetrahydro]-[2-H]-inden-1',3'-dione (**117**)

A solution of **89** (10.0 mg, 0.0438 mmol) and diene **104** (60.0 mg, 0.191 mmol) in dichloromethane (1.2 mL) was taken up into a syringe and transferred to a small steel bellows. The bellows was completely filled with the solution, so as to remove all air from the vessel, sealed with a screw and copper washer, and subjected to a pressure of ca. 284,000 psi* for 55 h. The exterior of the vessel was washed with hexane before it was opened and the solution was transferred to a flask. The inside of the bellows was rinsed with dichloromethane (2 × ca. 1 mL) and the combined solutions were evaporated. Flash chromatography of the residue twice over silica gel (1 × 15 cm) first with 2:1 hexane – ethyl acetate and then with

*Due to technical problems with the high pressure apparatus we are not certain of this measurement.

5:1 hexane – ethyl acetate gave **117** (11.4 mg, 48%) as a mixture of isomers. Three isomers were detected by TLC (silica, 5:1 hexane – ethyl acetate, R_f = 0.60, 0.22, 0.42) and one of these (R_f = 0.42) was cleanly separated from the others (3.4 mg): FTIR (CCl_4, cast) 2952.4, 2928.8, 2856.0, 1726.7, 1479.9, 1255.8, 1082.4, 1052.1, 877.1, 837.0, 776.4 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ7.16 (t, J = 7.5 Hz, 1H), 6.85 (d, J = 7.0 Hz, 1H), 6.59 (d, J = 8.0 Hz, 1H), 6.00 (s, br, 2H), 4.59 (m, 2H), 3.67 (s, 3H), 3.44 (dd, J = 4.5, 2.0 Hz, 2H), 3.05 (t, J = 7.0 Hz, 2H), 2.34 (t, J = 7.0 Hz, 2H), 0.89 (s, 18H), 0.11 (s), 0.09 (s). The signals at δ0.11 and 0.09 together have an area that corresponds to 12H. ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ213.0, 154.1, 148.3, 133.6, 129.9, 117.5, 108.5, 68.1, 64.5, 55.4, 52.7, 34.4, 32.4, 26.0, 18.4, -4.6, -4.8; mass spectrum (CI), m/z 560 (M+18). The ^1H and ^{13}C NMR spectra of the mixture of the other two isomers (8.0 mg) were recorded: ^1H NMR ($CDCl_3$, 400 MHz): The spectrum showed the presence of two diastereoisomers in a ratio of ca. 3.5:1. δ7.22 (t, J = 7.5 Hz), 7.20 (t, J = 7.5 Hz), 6.90 (m, 0.92H), 6.64 (d, J = 7.5 Hz, 0.92H), 5.73 (s, 1.45H), 5.67 (s, 0.40H), 4.50 (dd, J = 3.0, 1.5 Hz, 1.8H), 4.33 (dd, J = 3.0, 1.0 Hz, 0.5H), 3.72 (s, 0.66H), 3.65 (s, 2.1H), 3.44 (dd, J = 3.0, 1.5 Hz, 0.5H), 3.18 (m, 3.15H), 2.38 (t, J = 7.0 Hz), 2.35 (t, J = 7.5 Hz), 0.89 (s, 18H),

0.09 (s), 0.06 (s), 0.053 (s), 0.048 (s). The signals at δ7.22 and 7.20 together have an area that corresponds to 1.05 H; those at δ2.38 and 2.35 to 1.97H, and those at δ0.09, 0.06, 0.053 and 0.048 to 12H. ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ213.0, 212.5, 154.1, 148.6, 132.0, 131.2, 130.3, 130.2, 128.8, 117.8, 117.7, 108.8, 108.6, 67.0, 63.7, 63.1, 55.3, 55.1, 54.2, 52.9, 38.6, 36.2, 32.9, 32.4, 25.9, 25.8, 18.1, -4.41, -4.61, -4.64, -4.70.

Attempted Diels-Alder reaction of **89** and **77**

A mixture of spirocyclopentendione **89** (12.1 mg, 0.053 mmol) and 2,5-bis-(trimethylsiloxy)furan **77**[56] (300 mg, 1.22 mmol) was stirred at 80°C under argon for 12 h. Toluene (0.5 mL) was added [so as to wash the sublimed material from the walls of the condensor into the reaction flask] and stirring was continued at 80°C for an additional 10 h. The reaction mixture was cooled to room temperature and wet acetonitrile (0.5 mL, 50% aqueous acetonitrile) and tetrabutylammonium fluoride (2.5 mL, 1 M in THF, 2.5 mmol) were added. The mixture was stirred at room temperature overnight, diluted with water (ca. 10 mL), and extracted with chloroform (2 × ca. 15 mL). The combined extracts were dried and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) with 2:1 hexane – ethyl acetate allowed recovery of **89**

(5.9 mg, 49%) as the only major reaction component.

2,3-Dihydro-7-methoxy-1-[hydroxy[2-(phenylethynyl)phenyl]-methyl]-1H-indene-1-carboxylic acid (**124**)

Carboxylic acid **65** (29.1 mg, 0.1513 mmol) in THF (2.0 mL plus 1.0 mL rinse) was added dropwise over 2 min to a cold (-78°C) solution of LDA (0.60 mL, 0.60 M stock solution, 0.36 mmol) under argon. The bright yellow mixture was stirred at -78°C for 1 h and then kept at 50°C for 1 h. The mixture was then cooled to -78°C and a solution of aldehyde **122**[75] (35.1 mg, 0.1703 mmol) in THF (1.0 mL plus 0.5 mL rinse) was injected quickly. The reaction mixture was stirred at -78°C for 1.5 h, warmed to room temperature, and quenched by addition of saturated aqueous ammonium chloride (ca. 4 mL). Water (ca. 4 mL) was added and the aqueous layer was extracted with ether (2 × ca. 20 mL). The combined extracts were washed with water (1 × ca. 10 mL) and brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) with 1:2 hexane – ethyl acetate gave β-hydroxyacid **124** (25.9 mg, 42%) as a mixture of diastereoisomers: mp 116-133°C; FTIR (CCl_4, cast) 2940, 1697.4, 1265.2, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) showed the presence of two diastereoisomers in a ratio of ca. 1.3:1; δ7.76 (d, J = 8.0 Hz, 0.43H), 7.55 (m, 1.08H), 7.44

(dd, J = 1.0, 7.5 Hz, 0.51H), 7.33 (m, 4.59H), 7.20 (m, 2.15H), 7.02 (dt, J = 1.0, 7.5 Hz, 0.65H), 6.81 (d, J = 8.0 Hz, 0.57H), 6.73 (d, J = 7.5 Hz, 0.57H), 6.67 (t, J = 8.0 Hz, 1.0H), 6.56 (d, J = 7.5 Hz, 0.43H), 6.21 (s, 0.57H), 5.98 (s, 0.43H), 3.84 (s, 1.86H), 3.47 (s, 1.43H), 2.74 (m, 1.51H), 2.59 (m, 0.72H), 2.39 (m, 1.15H), 2.23 (m, 0.57H), 1.80 (m, 0.72H). No change in the ^1H NMR spectrum was detected upon addition of D_2O, but treatment of **124** with an etheral solution of diazomethane gave β-hydroxyester **125** as a mixture of diastereoisomers: [^1H NMR ($CDCl_3$, 400 MHz) δ7.84 (d, J = 8.0 Hz, 0.47H), 7.54 (m, 1.30H), 7.41 (dd, J = 1.0, 7.5 Hz, 0.71H), 7.33 (m, 3.89H), 7.21 (t, J = 8.0 Hz), 7.16 (dt, J = 1.0, 7.5 Hz), 7.01 (dt, J = 1.0, 8.0 Hz, 0.53H), 6.76 (t, J = 7.0 Hz, 1.12H), 6.64 (d, J = 8.0 Hz, 0.53H), 6.56 (d, J = 8.0 Hz, 0.35H), 6.45 (d, J = 8.0 Hz, 0.35H), 6.18 (d, J = 5.0 Hz, 0.53H), 6.01 (br d, J = 2.0 Hz, 0.41H), 5.11 (d, J = 2.5 Hz, 0.41H), 4.46 (d, J = 5.0 Hz, 0.59H), 3.765 (s), 3.755 (s), 3.68 (s, 1.30H), 3.36 (s, 1.18H), 2.85 (m, 0.53H), 2.71 (m, 0.59H), 2.53 (m, 0.94H), 2.31 (m, 0.47H), 1.50 (m, 0.65H). The signals at δ7.21 and δ7.16 together have an area which corresponds to 1.47H and those at δ3.765 and δ3.755 together have an area which corresponds to 4.60H. Upon D_2O exchange the doublets at δ5.11 and δ4.46 disappear and the signals at δ6.01 and δ6.18 sharpen to

singlets]. ^{13}C NMR (acetone-d_6, 100.61 MHz) δ179.1, 158.0, 149.0, 147.6, 143.0, 132.5, 132.32, 132.26, 132.15, 132.11, 132.0, 130.4, 130.2, 129.44, 129.38, 129.26, 129.18, 129.06, 128.5, 128.4, 128.04, 127.97, 124.7, 123.7, 118.1, 117.4, 110.4, 109.8, 94.6, 93.7, 89.0, 74.8, 73.2, 64.0, 56.2, 55.9, 35.3, 32.6, 32.4, 31.7; exact mass, m/z 398.1507 (calcd for $C_{26}H_{22}O_4$, m/z 398.1518).

Methyl 2,3-dihydro-7-methoxy-1-[hydroxy[2-(phenylethynyl]-phenyl]methyl]-1H-indene-1-carboxylate (**125**)

Ester **70** (113.1 mg, 0.5483 mmol) in THF (1.0 mL plus 1.0 mL rinse) was added dropwise over 10 min to a cold (-78°C) solution of LDA (1.4 mL, 0.64 M stock solution, 0.90 mmol) under argon. The solution was stirred at -78°C for 1 h before a solution of aldehyde **122**[75] (152.5 mg, 0.740 mmol) in THF (1.0 mL plus 0.5 mL rinse) was added rapidly. Stirring was continued for 1 h at -78°C and then at 0°C for 20 min and the mixture was then quenched with saturated aqueous ammonium chloride (ca. 4 mL). Water (ca. 4 mL) was added, the aqueous layer was extracted with ether (2 × ca. 20 mL) and the combined extracts were washed with 5% aqueous sodium bicarbonate (1 × ca. 10 mL) and brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue twice over silica gel (2 × 15 cm), first with 5:1 hexane – ethyl acetate and,

secondly, with 6:1 hexane – ethyl acetate gave ester **70** (16.4 mg, 14.5% recovery), aldehyde **122** (32.2 mg), and β-hydroxyester **125** (177.9 mg, 78.6%) as a mixture of diastereoisomers. **125**: mp 48-50°C; FTIR (CH_2Cl_2, cast) 3480, 1724.2, 1478.0, 1261.1, 1081.2, 757.8 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) showed the presence of two diastereoisomers in a ratio of ca. 9:1; δ7.84 (d, J = 8.0 Hz, 0.20H), 7.54 (m, 1.64H), 7.41 (dd, J = 1.0, 7.5 Hz, 1.1H), 7.33 (m, 3.3H), 7.21 (t, J = 8.0 Hz), 7.16 (dt, J = 1.0, 7.5 Hz), 7.01 (dt, J = 1.0, 8.0 Hz, 0.92H), 6.76 (t, J = 7.0 Hz, 1.74H), 6.64 (d, J = 8.0 Hz, 0.87H), 6.56 (d, J = 8.0 Hz, 0.10H), 6.45 (d, J = 8.0 Hz, 0.10H), 6.18 (d, J = 5.0 Hz, 0.82H), 6.01 (br d, J = 2.0 Hz, 0.10H), 5.11 (d, J = 2.5 Hz, 0.10H), 4.46 (d, J = 5.0 Hz, 0.87H), 3.765 (s), 3.755 (s), 3.68 (s, 0.36H), 3.36 (s, 0.31H), 2.85 (m, 0.10H), 2.71 (m, 0.82H), 2.53 (m, 0.92H), 2.31 (m, 1.13H), 1.50 (m, 0.95H). The signals at δ7.21 and δ7.16 together have an area which corresponds to 2.26H, and those at δ3.765 and δ3.755 together have an area that corresponds to 5.2H. Upon D_2O exchange the doublets at δ4.46 and δ5.11 disappeared and the signals at δ6.01 and δ6.18 collapsed to singlets. ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ176.5, 156.6, 148.4, 142.1, 141.1, 131.6, 131.4, 129.8, 129.5, 129.2, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.3, 127.2, 123.5, 122.6, 117.6, 116.8,

109.1, 108.5, 94.1, 88.1, 74.5, 64.5, 55.8, 55.4, 52.4, 52.2, 34.6, 31.7, 31.2;* exact mass, m/z 412.1674 (calcd for $C_{27}H_{24}O_4$, m/z 412.1674). Anal. calcd for $C_{27}H_{24}O_4$: C, 78.62; H, 5.86. Found: C, 78.66; H, 5.93.

Methyl 2,3-dihydro-7-methoxy-1-[2-(phenylethynyl)benzoyl]-1H-indene-1-carboxylate (**126**)

Chromic acid[53] (ca. 0.5 mL, 2.7 M) was added dropwise to a cold (0°C) solution of β-hydroxyester **125** (23.7 mg, 0.0574 mmol) in acetone (2 mL). The reaction mixture was stirred at room temperature for 2.5 h, water (ca. 10 mL) was added and the aqueous solution was extracted with ether (2 × ca. 20 mL). The combined extracts were washed with brine (1 × ca. 15 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) with 3:1 hexane – ethyl acetate gave β-ketoester **126** (20 mg, 85%): FTIR (CCl_4, cast) 1729.9, 1699.6, 1591.0, 1481.2, 1441.5, 1270.6, 1236.7, 1085.8, 787.4, 758.3 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ7.44 (m, 4H), 7.31 (m, 4H), 7.26 (dt, J = 1.5, 7.0 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 6.75 (d, J = 7.5 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 3.70 (s, 3H), 3.53 (s, 3H), 2.96 (m, 3H), 2.78 (m, 1H); ^{13}C NMR

*Not all of the carbon signals of the two diastereoisomers are resolved in this spectrum.

($CDCl_3$, 100.61 MHz) δ 200.9, 172.6, 156.3, 147.2, 142.8, 132.3, 131.7, 130.5, 128.9, 128.6, 128.4, 128.3, 127.0, 126.3, 123.2, 120.9, 117.3, 109.2, 92.6, 87.2, 71.2, 55.2, 52.4, 37.0, 31.8; exact mass, m/z 410.1521 (calcd for $C_{27}H_{22}O_4$, m/z 410.1518).

Attempted hydrolysis of β-ketoester **126**

A mixture of β-ketoester **126** (54.8 mg, 0.1335 mmol) and 30% aqueous sodium hydroxide (2 mL) was stirred under reflux overnight. The orange solution was cooled to room temperature and acidified to pH 1 by addition of dilute hydrochloric acid (1 M). The mixture was extracted with ether (2 × ca. 20 mL) and the combined extracts were washed with water (1 × ca. 15 mL) and brine (1 × ca. 15 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) with 5:1 hexane – ethyl acetate followed by 2:1 hexane – ethyl acetate and, finally, 1:2 hexane – ethyl acetate gave a slightly impure (TLC) sample of **65** (18.0 mg) as the major product. The structure was confirmed by comparison (^1H NMR) with an authentic sample.

No reaction occurred when the hydrolysis was attempted under milder conditions [two phase mixture of ether and 30% aqueous sodium hydroxide, room temperature, 14 h; 80°C, 3 h (after evaporation of the ether)].

2-(Phenylethynyl)benzoic acid (**128**)

a) Chromic acid[53] (ca. 1.5 mL, 2.7 M) was added dropwise to a cold (0°C) solution of aldehyde **122**[75] (297.4 mg, 1.44 mmol) in acetone (8.0 mL) until an orange colouration persisted. The reaction mixture was warmed to room temperature and stirred for 3 h. Water (ca. 10 mL) was added and the aqueous solution was extracted with ether (2 × ca. 30 mL). The combined extracts were washed with water (1 × ca. 30 mL) and brine (1 × ca. 30 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm) with 2:1 hexane – ethyl acetate gave acid **128** (246.9 mg, 76%): mp 128-130°C; FTIR (CCl_4, cast) 1696.5, 1679.0, 1301.5, 1272.0, 753.7 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ10.1 – 9.6 (br s, 0.5H), 8.15 (dd, J = 1.0, 8.0 Hz, 1H), 7.70 (dd, J = 1.0, 7.0 Hz, 1H), 7.66 – 7.24 (m, 7H); exact mass, m/z 222.0677 (calcd for $C_{15}H_{10}O_2$, m/z 222.0681).

b) The aryl lithium species was prepared according to the procedure of reference 75: a solution of n-butyllithium (5.6 mL, 1.55 M in hexane, 8.67 mmol) was added dropwise, over 30 min to a cold (-40 to -30°C) solution of bromide **129**[75] (1.1061 g, 4.304 mmol) in ether (8.0 mL) under argon. The reaction mixture was stirred at -30°C for 45 min and then at 0°C for 1 h. Carbon dioxide

was bubbled through the mixture for 5 min. Water (ca. 10 mL) and ether (ca. 30 mL) were added and the mixture was extracted with 4% aqueous sodium hydroxide (2 × ca. 20 mL). The combined aqueous extracts were acidified to pH 1 with concentrated hydrochloric acid and the resulting suspension was cooled to -5°C overnight to allow the precipitate to settle. The yellow solid was collected and purified by flash chromatography over silica gel (4 × 15 cm) with 2:1 hexane – ethyl acetate to give **128** (519.8 mg, 54%); this material was identical to that made by oxidation of the corresonding aldehyde **122**.

2-(Phenylethynyl)benzoyl chloride (**130**)

Oxalyl chloride (0.65 mL, 0.946 g, 7.45 mmol) was added to a solution of acid **128** (536.8 mg, 2.415 mmol) in benzene (6.0 mL) under argon. The solution was stirred at room temperature for 13 h and the solvent and excess of reagent were evaporated. Kugelrohr distillation [123°C (0.200 mm)] of the residue provided acid chloride **130** (371.2 mg, 63.8%) as a yellow liquid: IR (film) 2220, 1780, 1755, 1195, 885, 825, 770, 760, 745, 708, 695, 665, 650 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ8.21 (d, J = 8.0 Hz, 1H), 7.74 – 7.30 (m, 8H); ^{13}C NMR ($CDCl_3$, 50.32 MHz) δ134.5, 134.0, 133.6, 133.1, 132.0, 129.0, 128.4, 128.1, 124.4, 122.7, 96.2, 87.2; exact mass, m/z 242.0311 (19.30%

of base peak; calcd for $C_{15}H_9O^{37}Cl$, m/z 242.0312) and m/z 240.0337 (58.51% of base peak; calcd for $C_{15}H_9O^{35}Cl$, m/z 240.0342). Anal. calcd for $C_{15}H_9OCl$: C, 74.85; H, 3.77. Found: C, 74.54; H, 3.96.

2,3-Dihydro-7-methoxy-1-[2-(phenylethynyl)benzoyl]-1H-indene (**127**)

Carboxylic acid **65** (207.4 mg, 1.079 mmol) in THF (3.0 mL plus 2 × 0.5 mL rinse) was added dropwise over 2 min to a cold (-78°C) solution of LDA (4.4 mL, 0.60 M stock solution, 2.64 mmol) under argon. The bright yellow mixture was stirred at -78°C for 1 h and then kept at 50°C for 1 h. It was then cooled to -78°C and a solution of acid chloride **130** (371.2 mg, 1.54 mmol) in THF (2.0 mL plus 1.0 mL rinse) was injected rapidly. The reaction mixture was stirred at -78°C for 20 min and then at 0°C for 20 min. At this stage it was brought to room temperature (over about 10 min) and quenched with saturated aqueous ammonium chloride (ca. 4 mL). Water (ca. 2 mL) and ether (ca. 4 mL) were added and stirring was continued for 2 h. The aqueous phase was extracted with ether (2 × ca. 30 mL) and the combined ether extracts were washed with water (1 × ca. 30 mL) and brine (1 × ca. 30 mL), dried, and evaporated. Preparative thin layer chromatography (5:1 hexane – ethyl acetate) of the residue

on silica gel, followed by extraction of the silica with dichloromethane, gave ketone **127** (211.8 mg, 55%): FTIR (CCl_4, cast) 1688.9, 1590.3, 1480.3, 1265.3, 1077.0, 756.6 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ7.67 (m, 2H), 7.40 (m, 7H), 7.20 (t, J = 8.0 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.65 (d, J = 8.0 Hz, 1H), 5.30 (dd, J = 8.5, 6.0 Hz, 1H), 3.62 (s, 3H), 3.16 (m, 1H), 2.95 (m, 1H), 2.50 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ205.0, 155.9, 146.9, 142.6, 133.4, 131.6, 130.7, 130.4, 129.1, 128.5, 128.39, 128.37, 128.0, 123.2, 121.3, 117.0, 108.2, 94.2, 88.2, 55.0, 53.4, 32.6, 30.7; exact mass, m/z 352.1461 (calcd for $C_{25}H_{20}O_2$, m/z 352.1463). A satisfactory analysis could not be obtained for this compound.

2,3-Dihydro-7-methoxy-1-[2-(phenylethynyl)benzoyl]-1-(phenylseleno)-1H-indene (**131**)

Ketone **127** (25.6 mg, 0.0726 mmol) in THF (0.75 mL plus 0.5 mL rinse) was added dropwise over 2 min to a cold (-78°C) solution of LDA (0.19 mL, 0.60 M stock solution, 0.114 mmol) under argon. The orange mixture was stirred at -78°C for 1 h before a solution of phenylselenenyl chloride[76] (0.14 mL, 0.90 M in THF, 0.126 mmol) was added. The mixture was stirred at -78°C for 50 min and then warmed to 0°C over 15 min before being quenched with saturated aqueous ammonium chloride (ca. 2 mL). Water

(ca. 5 mL) was added and the aqueous layer was extracted with ether (2 × ca. 20 mL). The combined extracts were washed with water (1 × ca. 10 mL) and brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the crude residue over silica gel (1 × 15 cm) with 5:1 hexane – ethyl acetate gave **131** (28.0 mg, 76%) as an unstable oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ7.50 (m, 3H), 7.29 (m, 8H), 7.16 (m, 2H), 7.09 (t, J = 7.8 Hz, 2H), 6.60 (d, J = 7.3 Hz), 6.58 (d, J = 8.3 Hz), 3.55 (s, 3H), 2.91 (m, 1H), 2.66 (m, 2H), 2.32 (m, 1H). The signals at δ6.60 and 6.58 together have an area which corresponds to 2H. Exact mass, m/z 508.0942 (calcd for $C_{31}H_{24}O_2{}^{80}Se$, m/z 508.0942).

2,3-Dihydro-7-methoxy-1H-indene-1-spiro-2'-(3'-benzylidene)-[2H]-inden-1'-one (**132**)

A refluxing solution (12 mL) of ketone **131** (110.6 mg, 0.2179 mmol) in benzene was maintained under a slight static pressure of argon. AIBN (8.3 mg, 0.0505 mmol) in benzene (5.0 mL) and triphenyltin hydride (122.3 mg, 0.3484 mmol) in benzene (5.0 mL) were added simultaneously over 10 h (syringe pump).[32] Refluxing was continued for a further 5 h and the solvent was then evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm) with 7:1 hexane – ethyl acetate gave **132** (66.2 mg, 85%). An analytical sample was obtained by recrystallization

from ethyl acetate: mp 183-190°C; FTIR (CCl_4, cast) 1715.0, 1479.7, 1266.3, 765.5 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) showed the presence of two diastereoisomers in a ratio of *ca.* 1:1; δ7.90 (d, J = 8.0 Hz, 0.40H), 7.85 (dt, J = 5.5, 2.0 Hz, 0.69H), 7.81 (d, J = 8.0 Hz, 0.30H), 7.68 (dt, J = 1.0, 7.0 Hz, 0.49H), 7.44 (t, J = 7.5 Hz, 0.54H), 7.33 (m, 4.4H), 7.22 (t, J = 7.5 Hz, 0.89H), 7.16 (t, J = 7.5 Hz, 0.40H), 7.06 (m, 1.58H), 6.94 (d, J = 7.5 Hz, 0.59H), 6.77 (m, 1.48H), 6.62 (d, J = 8.0 Hz, 0.54H), 6.52 (d, J = 8.0 Hz, 0.49H), 6.44 (s, 0.49H), 3.54 (s, 1.38H), 3.41 (s, 1.33H), 3.25 (m, 0.99H), 3.10 (m, 0.54H), 2.61 (m, 0.49H), 2.38 (m, 1.48H), 2.26 (m, 0.49H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ206.5, 155.6, 155.5, 151.0, 148.0, 147.7, 147.1, 144.4, 143.4, 137.9, 137.0, 136.1, 134.7, 134.4, 134.0, 133.0, 129.6, 129.5, 129.0, 128.8, 128.6, 128.5, 127.8, 127.4, 126.8, 125.2, 124.9, 123.8, 123.6, 120.4, 117.6, 117.2, 109.1, 108.6, 65.0, 63.3, 55.4, 55.3, 39.5, 35.6, 32.4, 32.3; exact mass, m/z 352.1456 (calcd for $C_{25}H_{20}O_2$, m/z 352.1463). Anal. calcd for $C_{25}H_{20}O_2$: C, 85.20; H, 5.72. Found: C, 84.96; H, 5.61.

2,3-Dihydro-7-methoxy-1H-indene-1-spiro-2'-[2H]-inden-1',3'-dione (**118**)

An ozone-oxygen stream was bubbled through a cold (*ca.* -60°C) solution of **132** (35.9 mg, 0.1018 mmol) in

chloroform (4.0 mL), until a blue-grey colouration persisted (ca. 5 min). The flask was removed from the cooling bath and argon was bubbled through the solution for 10 min. Dimethyl sulfide (1 mL) was added and the mixture was stirred at room temperature for 36 h. The solvent was evaporated and flash chromatography of the residue twice over silica gel (2 × 15 cm and 1 × 15 cm) with 5:1 hexane – ethyl acetate gave **118** (23.9 mg, 84%). Recrystallization from ethyl acetate provided an analytical sample: mp 160-163°C; FTIR (CCl_4, cast) 1740, 1705.4, 1592.1 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ8.03* (m, 2H), 7.88* (m, 2H), 7.23 (t, J = 8.0 Hz, 1H), 6.94 (dd, J = 7.5, 0.75 Hz, 1H), 6.57 (d, J = 8.0 Hz, 1H), 3.42 (s, 3H), 3.28 (t, J = 7.25 Hz, 2H), 2.46 (t, J = 7.25 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ202.8, 155.1, 148.4, 141.8, 135.4, 130.3, 129.3, 123.2, 117.5, 108.6, 64.8, 55.2, 35.0, 32.6; exact mass, m/z 278.0945 (calcd for $C_{18}H_{14}O_3$, m/z 278.0943). Anal. calcd for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07. Found: C, 77.34; H, 4.96.

3,6-Dimethoxy-2-(phenylethynyl)benzaldehyde (**140**)

Pyridine (15 mL) was added to a mixture of copper(I)

*Signals at δ8.03 and δ7.88 show the characteristic AA'BB' pattern.

phenylacetylide[79] (570.3 mg, 3.46 mmol) and iodoaldehyde[78] **139** (530.1 mg, 1.815 mmol) under argon. The mixture was stirred under reflux for 17 h, cooled to room temperature, acidified with dilute hydrochloric acid (ca. 50 mL, 1 M), and extracted with ether (2 × ca. 50 mL). The combined extracts were washed with dilute hydrochloric acid (1 × ca. 30 mL, 1 M), water (1 × ca. 30 mL), 5% aqueous sodium bicarbonate (1 × ca. 30 mL) and brine (1 × ca. 30 mL), dried, and evaporated. The residue was partially purified by flash chromatography over silica gel (3 × 15 cm) with 5:1 hexane – ethyl acetate followed by 1:1 hexane – ethyl acetate. The product was further purified by flash chromatography over silica gel (2 × 17 cm) with 3:1 hexane – ethyl acetate to give **140** (91.3 mg, 18.9%). Recrystallization from ethyl acetate provided an analytical sample: mp 97.5-100°C; FTIR (CCl_4, cast) 1689.6, 1480, 1265.6 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ10.66 (s, 1H), 7.61 (m, 2H), 7.35 (m, 3H), 7.06 (d, J = 9.0 Hz, 1H), 6.91 (d, J = 9.0 Hz, 1H), 3.87 (s), 3.85 (s). The signals at δ3.87 and δ3.85 together have an area that corresponds to 6H. ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ190.3, 154.9, 154.8, 131.8, 128.7, 128.3, 125.8, 123.1, 117.2, 115.3, 112.6, 100.4, 88.7, 56.8, 56.4; exact mass, m/z 266.0934 (calcd for $C_{17}H_{14}O_3$, m/z 266.0943). Anal. calcd for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30. Found: C, 76.56; H,

5.28.

Attempted oxidation of aldehyde **140**

Chromic acid[53] (2.7 M) was added dropwise to a cold (0°C) solution of acetylenic aldehyde **140** (90.5 mg, 0.386 mmol) in acetone (4 mL) until an orange colouration persisted and starting material was no longer detectable (TLC, silica, 3:1 hexane – ethyl acetate). The reaction mixture was warmed to room temperature and stirred for 2.5 h. Water (ca. 10 mL) was added and the mixture was extracted with ether (2 × ca. 30 mL) and dichloromethane (1 × ca. 30 mL). The combined extracts were washed with water (1 × ca. 30 mL) and brine (1 × ca. 30 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm) with 1:1 hexane – ethyl acetate gave small amounts of several compounds which were not identified. On the basis of ^{1}H NMR spectra, none was the required acid.

Methyl 3,6-dimethoxy-2-iodobenzoate (**141**)

a) Chromic acid[53] (ca. 1-2 mL, 2.7 M) was added dropwise to a cold (0°C) solution of iodoaldehyde **140**[78] (246.7 mg, 0.8446 mmol) in acetone (5 mL), until an orange colouration persisted. The reaction mixture was warmed to room temperature and stirred for 4 h. Water (ca. 10 mL)

was added and the aqueous solution was extracted with ether (3 × *ca.* 20 mL). The combined extracts were washed with water (1 × *ca.* 20 mL) and brine (1 × *ca.* 20 mL), dried, and evaporated. The residue was dissolved in anhydrous ether (5 mL) and cooled to 0°C. Ethereal diazomethane solution was added dropwise with stirring until a yellow colouration persisted. The excess of reagent was destroyed by addition of a little silica gel and the mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm) with 5:1 hexane – ethyl acetate gave **141** (36.2 mg, 13.3%): mp 113-115°C; FTIR (CCl_4, cast) 1731.6, 1473.6, 1427.6, 1277.6, 1257.6, 1230, 1052.4, 1025.3 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ6.89 (d, J = 9.0 Hz, 1H), 6.81 (d, J = 9.0 Hz, 1H), 3.97 (s, 3H), 3.85 (s, 3H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ167.6, 152.7, 150.9, 132.1, 112.2, 112.0, 85.6, 57.2, 56.8, 52.8; exact mass, m/z 321.9707 (calcd for $C_{10}H_{11}O_4I$, m/z 321.9702). Anal. calcd for $C_{10}H_{11}O_4I$: C, 37.29; H, 3.44; O, 19.87. Found: C, 37.40; H, 3.44; O, 19.86.

b) Chromic acid[53] (*ca.* 1-2 mL; 2.7 *M*) was added dropwise to a cold (0°C) solution of alcohol **138**[78] (54.9 mg, 0.1866 mmol) in acetone (2 mL) until an orange colouration persisted. The mixture was stirred at 0°C for 3 h, then warmed to room temperature and stirred for an

additional 24 h. Water (ca. 10 mL) was added and the mixture was extracted with ether (2 × ca. 20 mL). The combined extracts were washed with water (1 × ca. 10 mL) and brine (1 × ca. 10 mL), dried, and evaporated. The residue was dissolved in anhydrous ether (ca. 3 mL) and cooled to 0°C. Ethereal diazomethane solution was added dropwise with stirring until a yellow colouration persisted. The excess of reagent was destroyed by addition of a little silica gel and the mixture was filtered and then evaporated. Flash chromatography of the crude residue over silica gel (1 × 15 cm) with 5:1 hexane – ethyl acetate gave **141** (8.1 mg, 13.5%).

Methyl 3,6-dimethoxy-2-(phenylethynyl)benzoate (**142**)

Dry pyridine (20 mL) was added to a mixture of copper(I) phenylacetylide[79] (398.6 mg, 2.423 mmol) and ester **141** (360.0 mg, 1.118 mmol) under argon. The mixture was stirred under reflux for 17 h, cooled to room temperature, diluted with aqueous hydrochloric acid (ca. 50 mL, 1 M) and extracted with ether (2 × ca. 50 mL). The combined extracts were washed with dilute hydrochloric acid (2 × ca. 30 mL, 1 M) and brine (1 × ca. 30 mL), dried, and evaporated. Flash chromatography of the residue twice over silica gel (3 × 18 cm), first with 2:1 hexane – ethyl acetate and secondly with 5:1 hexane – ethyl

acetate, gave **142** (310.9 mg, 93.8%). Recrystallization from ethyl acetate provided an analytical sample: mp 139-141°C; FTIR (CH_2Cl_2, cast) 1729.7, 1482.2, 1281.1, 1255.6, 1232.8, 1073.1, 1063.5, 796.0, 766.4 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ7.51 (m, 2H), 7.33 (m, 3H), 6.90 (d, J = 9.0 Hz), 6.87 (d, J = 9.0 Hz), 3.96 (s, 3H), 3.88 (s, 3H), 3.81 (s, 3H). The doublets at δ6.95 and δ6.87 together have an area that corresponds to 2H. ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ167.0, 154.6, 150.5, 131.8, 128.5, 128.3, 128.2, 123.4, 113.5, 113.2, 112.3, 97.3, 82.9, 57.0, 56.9, 52.4; exact mass, m/z 296.1042 (calcd for $C_{18}H_{16}O_4$, m/z 296.1049). Anal. calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 72.97; H, 5.57.

N,N-Diethyl-2,5-dimethoxybenzamide (**144**)

Diethylamine (0.20 mL, 144.5 mg, 1.98 mmol) was added to a cold (-30°C) solution of 2,5-dimethoxybenzoyl chloride (305.0 mg, 1.520 mmol) in THF (3.0 mL) under argon. The mixture was stirred for 10 min at -30°C and the cooling bath was then removed. Stirring was continued at room temperature for 45 min, 5% aqueous sodium hydroxide (ca. 10 mL) was added and the mixture was extracted with ether (2 × ca. 20 mL). The combined extracts were washed with brine (1 × ca. 20 mL), dried, and evaporated. Flash chromatography of the residue over

silica gel (2 × 15 cm) with 1:1 hexane – ethyl acetate gave **144** (336.6 mg, 93.3%): mp 84-86°C; FTIR (CH_2Cl_2, cast) 1628.6, 1584.9 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ6.86 (br d, J = 2.0 Hz, 2H), 6.77 (m, 1H), 3.774 (s), 3.768 (s), 3.57 (m, 2H), 3.17 (q, J = 7.0 Hz, 2H), 1.25 (t, J = 7.0 Hz, 3H), 1.06 (t, J = 7.0 Hz, 3H). The signals at δ3.774 and δ3.768 together have an area that corresponds to 6H. ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ168.3, 153.7, 149.3, 127.8, 114.9, 113.1, 112.5, 56.3, 55.8, 42.7, 38.8, 13.9, 12.8; exact mass , m/z 237.1364 (calcd for $C_{13}H_{19}O_3N$, m/z 237.1364).

N,N-Diethyl-3,6-dimethoxy-2-(phenylethynyl)benzamide (**146**)

sec-Butyllithium (1.9 mL, 0.7 M in cyclohexane, 1.3 mmol) was added over 5 min to a cold (-78°C) solution of amide **144** (278.6 mg, 1.174 mmol) and tetramethylethylenediamine (0.20 mL, 154 mg, 1.32 mmol) in THF (4.0 mL) under argon.[80,81] The bright yellow solution was stirred at -78°C for 1 h and 1-chloro-2-iodoethane[78] (0.14 mL, 296.8 mg, 1.60 mmol) was then added. The flask was transferred from the dry-ice acetone bath to an ice-water bath and stirring was continued at 0°C for 2 h. Water (ca. 10 mL) was added and the mixture was extracted with ether (2 × ca. 20 mL). The combined ether extracts were washed with water (1 × ca. 10 mL) and brine (1 × ca. 10

mL), dried, and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm) with 1:1 hexane – ethyl acetate gave an apparently homogeneous (TLC, silia, 1:1 hexane – ethyl acetate) solid (342.3 mg). ^{1}H NMR ($CDCl_3$, 400 MHz) showed the presence of iodoamide **145** (see subsequent experiment for spectral data) and starting material **144** in a ratio of ca. 5.6:1.

Dry pyridine (3.0 mL) was added to a portion (175.9 mg) of the mixture of amides and copper(I) phenylacetylide[79] (219.5 mg, 1.334 mmol) under argon. The reaction mixture was stirred at reflux for 20 h, cooled to room temperature, diluted with water (ca. 10 mL), and extracted with ether (3 × ca. 25 mL). The combined extracts were washed with brine (1 × ca. 25 mL), dried, and evaporated. Flash chromatography of the residue twice over silica gel (2 × 15 cm) with 1:1 hexane – ethyl acetate gave amide **144** (13.3 mg, 4.8% recovery of starting material) and N,N-diethyl-3,6-dimethoxy-2-(phenylethynyl)-benzamide **146** (113.4 mg, 55.7% overall yield from amide **144**). Recrystallization from ether – ethyl acetate provided an analytical sample: mp 152-153.5°C; FTIR (CH_2Cl_2, cast) 1635.9, 1474.3, 1260.2 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ7.49 (m, 2H), 7.29 (m, 3H), 6.87 (d, J = 9.0 Hz, 1H), 6.88 (d, J = 9.0 Hz, 1H), 3.90 – 3.74 [m (containing 2 singlets at δ3.88 and δ3.78), 7H], 3.41 (m, 1H), 3.21

(m, 2H), 1.23 (t, J = 7.0 Hz, 3H), 1.08 (t, J =7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ166.5, 154.7, 149.7, 131.7, 131.2, 128.23, 128.15, 123.5, 112.8, 111.9, 111.5, 96.8, 83.2, 56.8, 56.6, 42.8, 38.9, 13.8, 13.0; exact mass, m/z 337.1671 (calcd for $C_{21}H_{23}O_3N$, m/z 337.1678). Anal. calcd for $C_{21}H_{23}O_3N$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.53; H, 6.67; N, 4.12.

N,N-Diethyl-3,6-dimethoxy-2-iodobenzamide (**145**)

sec-Butyllithium (0.44 mL, 1.5 M in cyclohexane, 0.66 mmol) was added over 5 min to a cold (-78°C) solution of amide **144** (118.9 mg, 0.501 mmol) and tetramethylethylenediamine (0.10 mL, 77 mg, 0.66 mmol) in THF (3.0 mL) under argon.[80,81] The bright yellow solution was stirred at -78°C for 30 min, at 0°C for 30 min, and then cooled to -78°C. 1-Chloro-2-iodoethane[78] (0.070 mL, 148 mg, 0.779 mmol) was added and the flask was transferred to an ice-water bath. Stirring was continued at 0°C for 2 h, and the mixture was diluted with water (ca. 10 mL) and extracted with ether (2 × ca. 20 mL). The combined extracts were washed with water (1 × ca. 10 mL) and brine (1 × ca. 10 mL), dried, and evaporated to give **145** (179.2 mg, 98.5%). Recrystallization from ethyl acetate – ether afforded an analytical sample: mp 118.5-123°C; FTIR (CCl_4, cast) 1635.7, 1468.6, 1428.9, 1258.4 cm^{-1}; ^1H NMR

($CDCl_3$, 200 MHz) δ6.88 (d, J = 9.0 Hz, 1H), 6.76 (d, J = 9.0 Hz, 1H), 3.98 – 3.80 [m (singlet at δ3.84), 4H] 3.77 (s, 3H), 3.36 (m, 1H), 3.14 (q, J = 7.0 Hz, 2H), 1.29 (t, J = 7.0 Hz, 3H), 1.08 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ167.6, 152.8, 150.2, 133.9, 111.8, 110.8, 87.0, 57.1, 56.4, 42.6, 38.7, 13.6, 12.4; exact mass, m/z 363.0345 (calcd for $C_{13}H_{18}NO_3I$, m/z 363.0332). Anal. calcd for $C_{13}H_{18}NO_3I$: C, 42.99; H, 5.00; N, 3.86. Found: C, 43.26; H, 5.02; N, 3.76.

Attempted reaction of **71** with **146**

Carboxylic acid **65** (27.8 mg, 0.1446 mmol) in THF (2.0 mL plus 1.0 mL rinse) was added dropwise over 2 min to a cold (-78°C) solution of LDA (0.50 mL, 0.69 M stock solution, 0.347 mmol) under argon. The resultant bright yellow mixture was stirred at -78°C for 1.25 h and then kept at 50°C for 1 h. It was cooled to -78°C and then transferred under argon to a cold (-78°C) suspension of amide **146** (59.5 mg, 0.1763 mmol) in THF (2.0 mL). The mixture was stirred at -78°C for 20 min and then at 0°C for 40 min and, finally, at room temperature for 1.5 h before being quenched with saturated aqueous ammonium chloride (ca. 2 mL). Water ca. 2 mL) and ether (ca. 4 mL) were added and stirring was continued for 4 h. The mixture was extracted with ether (2 × ca. 30 mL) and

dichloromethane (1 × ca. 30 mL). The combined extracts were washed with brine (1 × ca. 15 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm) with 1:1 hexane – ethyl acetate gave unreacted amide **146** (50.5 mg, 85% recovery) as the only major reaction component.

N-(2-Hydroxy-1,1-dimethylethyl)-2,5-dimethoxybenzamide (**147**)

The general procedure of reference 88 was used: 2,5-dimethoxybenzoyl chloride **80** (455.9 mg, 2.27 mmol) in dichloromethane (1.0 mL plus 0.5 mL rinse) was added dropwise over ca. 2 min to a cold (0°C) solution of 2-amino-2-methyl-propan-1-ol (570.0 mg, 6.39 mmol) in dichloromethane (1.5 mL) and the mixture was stirred at room temperature for 24 h. The white solid was collected and washed successively with water (ca. 10 mL), 5% aqueous hydrochloric acid (ca. 10 mL), 5% aqueous sodium hydroxide (ca. 10 mL) and water (ca. 10 mL). Recrystallization from ether provided hydroxyamide **147** [203.1 mg, 35.3% (not optimized)] as small white crystals: mp 112-113.5°C; FTIR (nujol) 3398.9, 3371.9, 1642, 1637.0, 1605.7, 1552.0, 1497.8, 1215.7, 1182.5, 1067.2, 1046.9, 831.9, 727.1 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ8.28 [br ($W_{1/2}$ = 8.0 Hz), 1H], 7.74 (d, J = 3.0 Hz, 1H), 7.03 (dd, J = 3.0, 9.0 Hz, 1H),

6.93 (d, J = 9.0 Hz, 1H), 5.18 (t, J = 6.0 Hz, 1H), 3.93 (s, 3H), 3.83 (s, 3H), 3.69 (d, J = 6.0 Hz, 2H), 1.40 (s, 6H). Upon D_2O exchange the doublet at δ3.69 disappeared and the triplet at δ5.18 simplified to a broad singlet. ^{13}C NMR (100.61 MHz) δ165.5, 154.1, 151.6, 122.3, 119.7, 115.3, 113.3, 71.0, 56.7, 56.1, 55.8, 24.9; exact mass, m/z 253.1311 (calcd for $C_{13}H_{19}O_4N$, m/z 253.1314). Anal. calcd for $C_{13}H_{19}O_4N$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.49; H, 7.56; N, 5.47.

2-(2,5-Dimethoxyphenyl)-4,5-dihydro-4,4-dimethyloxazole (148)

The general procedure of reference 88 was used: a solution of hydroxyamide **147** (203 mg, 0.802 mmol) in thionyl chloride (0.50 mL, 815 mg, 6.85 mmol) was stirred at room temperature for 30 min. Ether (9 mL) was added and the resulting pale yellow solid was collected, washed with ether (1 mL), and dissolved in water (15 mL). Aqueous sodium hydroxide (25% w/v, 2 mL) was added and the mixture was extracted with ether (2 × 20 mL). The combined extracts were washed with water (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm) with 1:1 hexane – ethyl acetate gave 2-(2,5-dimethoxyphenyl)-4,5-dihydro-4,4-dimethyloxazole **148** (156.0 mg, 82.7%). Kugelrohr

distillation [85°C (0.12 mm)] provided an analytical sample: mp 32-36°C; FTIR (CCl_4, cast) 1500.8, 1225.4, 1043.4 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ7.27 [m, (overlaps with $CHCl_3$ signal), 1H], 6.97 (dd, J = 9.0, 3.0 Hz, 1H), 6.89 (d, J = 9.0 Hz, 1H), 4.10 (s, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 1.39 (s, 6H); ^{13}C NMR ($CDCl_3$, 100.614 MHz) δ161.1, 153.2, 152.7, 118.2, 115.7, 113.7, 79.0, 67.5, 57.0, 55.9, 28.4; exact mass, m/z 235.1209 (calcd for $C_{13}H_{17}O_3N$, m/z 235.1209). Anal. calcd for $C_{13}H_{17}O_3N$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.51; H, 7.26; N, 5.99.

2-(3,6-Dimethoxy-2-iodophenyl)-4,5-dihydro-4,4-dimethyloxazole (**149**)

The general procedure of reference 87 was used: n-butyllithium (0.17 mL, 1.55 M in hexane, 0.264 mmol) was added dropwise over ca. 2 min to a cold (-78°C) solution of dihydrooxazole **148** (55.4 mg, 0.2354 mmol) in DME (2.0 mL) under argon and the solution was stirred at -78°C for 1.5 h. 1-Chloro-2-iodoethane[78] (0.030 mL, 64 mg, 0.334 mmol) was added and stirring was continued at -78°C for 15 min, at 0°C for 15 min, and at room temperature for 15 min. Saturated aqueous ammonium chloride (5 mL) and water (ca. 5 mL) were added and the mixture was extracted with ether (2 × ca. 20 mL). The combined extracts were washed

with brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) with 2:1 hexane – ethyl acetate followed by 1:1 hexane – ethyl acetate, allowed separation of unreacted starting material (17.6 mg, 31.8% recovery) from the product **149** (16.4 mg, 19.3%). Recrystallization from ethyl acetate provided an analytical sample: mp 119-120°C; FTIR (CH_2Cl_2, cast) 2966.4, 1673.4, 1476.3, 1435.5, 1415.0, 1300.8, 1291.4, 1260.9, 1095.2, 1038.2 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ6.92 (d, J = 8.0 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 4.17 (s, 2H), 3.84 (s, 3H), 3.80 (s, 3H), 1.46 (s, 6H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ160.7, 152.9, 152.7, 126.8, 112.8, 112.3, 90.4, 79.5, 68.3, 57.3, 57.1, 28.2; exact mass, m/z 361.0170 (calcd for $C_{13}H_{16}O_3NI$, m/z 361.0175). Anal. calcd for $C_{13}H_{16}O_3NI$: C, 43.23; H, 4.465; N, 3.88; O, 13.29. Found: C, 42.86; H, 4.42; N, 3.83; O, 13.37.

Methyl (Z)-3-iodopropenoate (**150**)

(Z)-3-Iodoacrylic acid was prepared by a literature procedure:[89] propiolic acid (1.53 mL, 1.74 g, 24.8 mmol) in THF (3.0 mL) was added to methylmagnesium iodide [prepared from magnesium turnings (1.99 g, 81.8 mmol) and methyl iodide (4.63 mL, 10.55 g, 74.4 mmol) in THF (20 mL)]. The mixture was heated at reflux for 1 h, cooled to

0°C, and quenched by addition of glacial acetic acid (ca. 10 mL). Water (ca. 40 mL) was added and the mixture was exracted with ether (2 × ca. 40 mL). The combined extracts were washed with water (1 × ca. 30 mL) and brine (1 × ca. 30 mL), dried, and evaporated. The residue was dissolved in ether (ca. 20 mL) and the solution was cooled to 0°C. An excess of diazomethane was added. Silica gel was added to destroy the excess of reagent and the mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (4 × 15 cm) with 10:1 hexane – ethyl acetate gave methyl (Z)-3-iodopropenoate **150** (1.0896 g, 20.7%): IR (film) 1715, 1595, 1430, 1320, 1205, 1165, 1000, 910, 810 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ7.48 (d, J = 9.0 Hz, 1H), 6.93 (d, J = 9.0 Hz, 1H), 3.82 (s, 3H); exact mass, m/z 211.9337 (calcd for $C_4H_5O_2I$, m/z 211.9334).

Methyl (Z)-5-phenylpent-2-en-4-ynoate (**151**)

Pyridine (2.0 mL) was added to a mixture of copper(I) phenylacetylide[79] (280.1 mg, 1.703 mmol) and methyl (Z)-3-iodopropenoate (222.7 mg, 1.050 mmol) under argon. The mixture was stirred under reflux for 16 h, cooled to room temperature, acidified with dilute hydrochloric acid (ca. 20 mL, 1 M) and extracted with ether (2 × ca. 20 mL). The combined extracts were washed with dilute hydrochloric acid (2 × ca. 10 mL), water (1 × ca. 10 mL), and brine (1

× ca. 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm) with 10:1 hexane – ethyl acetate gave **151** (110.0 mg, 56.2%). Kugelrohr distillation [100°C (0.02 mm)] provided an analytical sample: IR (CCl_4) 2200, 1725, 1712, 1608, 1435, 1208, 1168, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ7.56 (m, 2H), 7.36 (m, 3H), 6.39 (d, J = 11.0 Hz, 1H), 6.19 (d, J = 11.0 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (100.61 MHz) δ165.1, 132.1, 129.2, 128.4, 127.9, 123.0, 122.8, 101.3, 86.4, 51.4; exact mass, m/z 186.0680 (calcd for $C_{12}H_{10}O_2$, m/z 186.0680). Anal. calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.04; H, 5.53.

Methyl 3,6-dihydroxy-2-(phenylethynyl)benzoate (**152**)

A mixture of **151** (71.3 mg, 0.3828 mmol) and 2,5-bis(trimethylsiloxy)furan[56] [0.50 mL (75.3% by GC, OF1, 180°C), ca. 375 mg, ca. 1.5 mmol] was stirred at 80°C under argon for 48 h and then cooled to room temperature. Aqueous acetonitrile (2.0 mL, 1:1 water – acetonitrile) and tetrabutylammonium fluoride (5 mL, 1 M in THF, 5 mmol) were added and stirring was continued overnight at room temperature. Water (ca. 10 mL) was added and the mixture was extracted with chloroform (2 × ca. 15 mL). The combined extracts were washed with brine (1 × ca. 10 mL), dried, and evaporated. Flash

chromatography of the residue twice over silica gel (2 × 15 cm), first with 3:1 hexane – ethyl acetate and secondly with 5:1 hexane – ethyl acetate (1 × 28 cm), allowed separation of unreacted starting material **151** (50.2 mg, 70.4% recovery) from the desired product **152** (6.6 mg, 6.4%). **152**: FTIR (CCl_4, cast) 3490, 1672.4, 1454.7, 1436.8, 1349.9, 1330.8, 1318.9, 1237.7, 1176.3, 1128.8, 819.3, 751.5, 688.3 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ10.9 (s, 1H), 7.57 (m, 2H), 7.44 (m, 3H), 7.20 (d, J = 9.0 Hz, 1H), 6.99 (d, J = 9.0 Hz, 1H), 6.02 (s, 1H), 4.02 (s, 3H). Upon D_2O exchange the signals at δ10.9 and δ6.02 disappeared. Exact mass, m/z 268.0732 (calcd for $C_{16}H_{12}O_4$, m/z 268.0736).

Methyl 3,6-dimethoxy-2-nitrobenzoate (**153**)

The procedure of reference 90 was used to prepare 3,6-dimethoxy-2-nitrobenzoic acid from 2,5-dimethoxybenzoic acid (1.316 g, 7.224 mmol) and nitric acid (5.5 mL, 70%). A cold (0°C) suspension of the crude product in ether (ca. 50 mL) was treated with diazomethane. The excess of reagent was destroyed by addition of silica gel. Dichloromethane (ca. 100 mL) was added and the mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (5 × 15 cm) with 2:1 hexane – ethyl acetate followed by 1:1 hexane –

ethyl acetate allowed separation of the meta- and para-nitrated products from the desired methyl 3,6-dimethoxy-2-nitrobenzoate **153** (1.2741, 73%): mp 119-121°C; FTIR (CH_2Cl_2, cast) 1741.6, 1581.1, 1529.2, 1493.7, 1460.2, 1449.9, 1441.8, 1365.7, 1304.9, 1291.8, 1271.3, 1249.1, 1135.1, 1053.0, 803.3, 728.7 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ7.11 (d, J = 9.5 Hz, 1H), 7.08 (d, J = 9.5 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ163.3, 150.9, 145.5, 139.9, 118.5, 116.3, 115.9, 103.6, 57.4, 57.2, 53.0; exact mass, m/z 241.0589 (calcd for $C_{10}H_{11}O_6N$, m/z 241.0586).

Methyl 2-amino-3,6-dimethoxybenzoate (**154**)

Ethyl acetate (20 mL) was added to a mixture of nitroester **153** (1.322 g, 5.482 mmol) and 5% palladium on charcoal (0.247 g). The suspension was stirred and maintained for 5 h at room temperature under hydrogen at a pressure of 10 psi. The mixture was filtered and the catalyst was washed with ethyl acetate (2 × *ca.* 10 mL). The combined filtrates were evaporated. Kugelrohr distillation of the residue provided an analytical sample of **154** (1.060 g, 91.5%): bp 115°C (0.005 mm); FTIR (CCl_4, cast) 3488.9, 3378.9, 1726.8, 1686.9, 1614.2, 1561.1, 1485.0, 1465.2, 1437.1, 1348.6, 1309.0, 1272.5, 1249.1, 1225.6, 1187.4, 1159.4, 1125.1, 1079.8, 1054.6, 798.4,

784.5, 720.3 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ6.74 (d, J = 9.2 Hz, 1H), 6.14 (d, J = 8.6 Hz, 1H), 5.43 (s, br, $W_{1/2}$ = 10 Hz, 2H), 3.90 (s, 3H), 3.80 (s, 3H), 3.78 (s, 3H). Upon D_2O exchange the broad singlet at δ5.43 disappeared. ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ168.5, 154.1, 141.8, 140.7, 113.0, 105.0, 98.7, 56.6, 56.3, 51.7; exact mass, m/z 211.0844 (calcd for $C_{10}H_{13}O_4N$, m/z 211.0844). Anal. calcd for $C_{10}H_{13}O_4N$: C, 56.87; H, 6.20; N, 6.63. Found: C, 56.76; H, 6.17; N, 6.45.

2-Amino-3,6-dimethoxybenzoic acid (**155**)

A mixture of ester **154** (457.2 mg, 2.164 mmol) and aqueous potassium hydroxide (2.0 mL, 5.15 M in water, 10.3 mmol) was stirred under reflux for 12 h and then cooled to room temperature. Water (ca. 10 mL) was added and the aqueous solution was carefully neutralized by addition of dilute hydrochloric acid. The mixture was extracted with dichloromethane (2 × ca. 20 mL). The combined extracts were washed with brine (1 × ca. 10 mL), dried, and evaporated to leave **155** (355.5 mg, 83.3%) as a white solid: mp 90-97.5°C (lit.[90] mp 97°C); FTIR (CH_2Cl_2, cast) 3477.3, 3358.9, 1695.7, 1621.5, 1551.5, 1472.4, 1461.6, 1360.1, 1271.8, 1224.9, 1115.9, 1054.1, 800.6 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ10.62 (s, 1H), 6.74 (d, J = 8.5 Hz), 6.67 (s, br, $W_{1/2}$ = 20.0 Hz), 3.97 (s, 3H), 3.84 (s,

3H). The signals at δ6.74 and 6.67 together have an area which corresponds to 3H. Upon D_2O exchange the signal at δ6.67 disappeared. Exact mass, m/z 197.0694 (calcd for $C_9H_{11}O_4N$, m/z 197.0688).

3,6-Dimethoxy-2-iodobenzoic acid (**143**)

The general procedure of reference 91 was used: aqueous sodium nitrite (4.5 mL, 1.45 mM, 6.52 mmol) was added over 20 min to a cold (0°C) solution of 2-amino-3,6-dimethoxybenzoic acid (1.2125 g, 6.149 mmol) in acidic methanol [conc H_2SO_4 (1.90 g) in MeOH (30 mL)]. The mixture was stirred at 0°C for a further 15 min before a cold (0°C) solution of potassium iodide (4.88 g, 29.4 mmol) in water (30 mL) was added. The mixture was then stirred at room temperature overnight. Dilute hydrochloric acid (ca. 100 mL, 1 M) was added and the mixture was extracted with dichloromethane (2 × ca. 150 mL). The combined extracts were dried and evaporated. Recrystallization from ethyl acetate, with the aid of decolourizing charcoal, gave 3,6-dimethoxy-2-iodobenzoic acid **143** (1.0293 g, 52%): mp 212-222°C; FTIR (nujol) 1720.7, 1662.6, 1572.1, 1479.8, 1423.7, 1300.6, 1275.8, 1261.3, 1240.0, 1055.0, 1024.1, 809.4, 715.2 cm^{-1}; ^1H NMR [acetone-d_6 (plus 1% D_2O), 200 MHz] δ7.07 (d, J = 9.0 Hz, 1H), 6.96 (d, J = 9.4 Hz, 1H), 3.82 (s, 3H), 3.77 (s, 3H);

exact mass, m/z 307.9554 (calcd for $C_9H_9O_4I$, m/z 307.9546).

Methyl 3,6-dimethoxy-2-iodobenzoate (**141**)

The general procedure of reference 91 was used: sodium nitrite (0.28 g, 4.20 mmol) in water (3.0 mL) was added over ca. 20 min to a cold (0°C) slurry of methyl 2-amino-3,6-dimethoxybenzoate (663.4 mg, 3.14 mmol) in 20% aqueous hydrochloric acid (4.5 mL). The mixture was stirred at 0°C for a further 20 min and a cold (0°C) solution of potassium iodide (2.6 g, 15.7 mmol) in water (13 mL) was then added. Stirring, at room temperature, was continued overnight. Water (ca. 30 mL) was added and the mixture was extracted with ether (2 × ca. 75 mL). The combined extracts were washed with 10% aqueous sodium bicarbonate (1 × ca. 50 mL), water (1 × ca. 50 mL), and brine (1 × ca. 50 mL), dried, and evaporated. Flash chromatography (three times) of the residue over silica gel [twice (3 × 20 cm) and once (2 × 20 cm)] with 5:1 hexane – ethyl acetate allowed separation of methyl 2,5-dimethoxybenzoate from methyl 3,6-dimethoxy-2-iodobenzoate **141** (487.5 mg, 48%). This material proved to be identical with that prepared from aldehyde **139**

3,6-Dimethoxy-2-(phenylethynyl)benzoic acid (**133**)

THF (15.0 mL) and water (21 μL, 21.0 mg, 1.14 mmol) were added to a mixture of ester **142** (91.1 mg, 0.3074 mmol) and potassium t-butoxide[84] (380.4 mg, 3.393 mmol). The mixture was stirred under reflux for 48 h, cooled to room temperature, diluted with water (ca. 15 mL), and extracted with ether (2 × ca. 15 mL). The aqueous layer was acidified to pH 1 by addition of dilute hydrochloric acid and back-extracted with ether (2 × ca. 20 mL). The combined extracts were washed with brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) with 1:2 hexane – ethyl acetate gave acid **133** (45.9 mg, 52.9%) as a pale yellow solid: mp 144-160°C; FTIR (CH_2Cl_2, cast) 3500-2700, 1735, 1704.1, 1492, 1481.3, 1294, 1261.2, 1071.6, 1059.6 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ7.53 (m, 2H), 7.26 (m, 3H), 6.95 (d, J = 8.9 Hz), 6.91 (d, J = 9.2 Hz), 3.90 (s, 3H), 3.85 (s, 3H). The signals at δ6.95 and δ6.91 together have an area which corresponds to 2H. Exact mass, m/z 282.0888 (calcd for $C_{17}H_{14}O_4$, m/z 282.0892). A small amount of acid **133** was treated with an excess of diazomethane. Chromatographic analysis of the product (R_f = 0.76, TLC, silica, 1:2 hexane – ethyl acetate) showed it to be the same as the ester **142**.

Attempted reaction of **71** and **142**

a) Acid **65** (88.8 mg, 0.4619 mmol) in THF (2.0 mL plus 2 × 0.5 mL rinse) was added dropwise over *ca.* 2 min to a cold (-78°C) solution of LDA (1.65 mL, 0.68 *M* stock solution, 1.12 mmol) under argon. The solution was stirred at -78°C for 1 h and at 50°C for 1 h. It was then cooled to -78°C and ester **142** (168.7 mg, 0.5693 mmol) in THF (2.0 mL plus 1.0 mL rinse) was injected quickly. The mixture was stirred at -78°C for 15 min, at 0°C for 1.25 h and at room temperature for 30 min. Saturated aqueous ammonium chloride (*ca.* 10 mL) and ether (*ca.* 10 mL) were added and stirring was continued at room temperature for 2 h. Dilute hydrochloric acid (*ca.* 10 mL, 1 *M*) was added and the mixture was extracted with ether (2 × *ca.* 20 mL). The combined extracts were washed with brine (1 × *ca.* 10 mL), dried, and evaporated. Analysis [TLC and ^{1}H NMR (200 MHz)] of the crude residue showed only the presence of starting materials **65** and **142**.

b) A solution of dianion **71*** (1.0 mL, 0.108 *M* in THF, 0.108 mmol) was added to a cold (-78°C) solution of eater **142** (45.7 mg, 0.1542 mmol) in THF (1.0 mL) under

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*The stock solution of dianion (**71**) was prepared from acid **65** and LDA in THF, according to the procedure described in the previous experiment.

argon. The mixture was stirred at room temperature for 1 h, and at 50°C for 2 h and was then cooled to room temperature. Saturated aqueous ammonium chloride (ca. 1 mL) was added and the mixture was transferred to an Erlenmeyer flask. Water (ca. 5 mL) and ether (ca. 5 mL) were added. The mixture was stirred at room temperature overnight and then diluted with water (ca. 10 mL) and extracted with ether (2 × ca. 20 mL). The combined extracts were washed with brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue allowed partial separation of the reaction components. The ^{1}H NMR (200 MHz) spectrum of the mixed fractions showed starting material **142** to be the major component. Signals corresponding to the diisopropyl amide derived from ester **142** were also present.

2,3-Dihydro-1-(2,5-dimethoxybenzoyl)-7-methoxy-1H-indene (**158**)

Acid **65** (24.8 mg, 0.129 mmol) in THF (1.0 mL plus 2 × 0.5 mL rinse) was added dropwise over ca. 2 min to a cold (-78°C) solution of LDA (0.46 mL, 0.68 M stock solution, 0.313 mmol) under argon. The solution was stirred at -78°C for 1 h and at 50°C for 1 h before being cooled to -78°C. Ester **141** (144.7 mg, 0.4492 mmol) in THF (1.0 mL plus 1.0 mL rinse) was injected quickly and the mixture

was stirred at 0°C for 1 h, and at 70°C for 3 h. The mixture was cooled to room temperature, quenched with saturated aqueous ammonium chloride (ca. 5 mL), and then stirred for an additional 1 h. Water (ca. 10 mL) was added and the mixture was extracted with ether (2 × ca. 20 mL). The combined extracts were washed with brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue twice over silica gel (2 × 15 cm and 1 × 15 cm) with 5:1 hexane – ethyl acetate allowed separation of unreacted starting material **141** (131.8 mg, 91% recovery) from ketone **158** (4.7 mg, 11.7%). **158**: FTIR (CH_2Cl_2, cast) 2952.9, 2942.9, 2835.8, 1679.7, 1603.4, 1588.5, 1495.6, 1478.9, 1464.3, 1450.9, 1439.5, 1419.9, 1335.2, 1305.6, 1280.0, 1262.7, 1225.1, 1194.2, 1167.6, 1147.3, 1076.5, 1051.6, 1026.3, 1018.8, 880.2, 811.5, 778.8 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ7.18 (m, 2H), 7.03 (dd, J = 3.0, 9.0 Hz, 1H), 6.91 (m, 2H), 6.66 (d, J = 8.0 Hz, 1H), 5.04 (dd, J = 5.0, 9.0 Hz, 1H), 3.88 (s, 3H), 3.78 (s, 3H), 3.66 (s, 3H), 3.01 (m, 2H), 2.63 – 2.22 (m, 2H); exact mass, m/z 312.1366 (calcd for $C_{19}H_{20}O_4$, m/z 312.1361).

3,6-Dimethoxy-2-iodobenzoyl chloride (**156**)

A mixture of 3,6-dimethoxy-2-iodobenzoic acid (186.3 mg, 0.6047 mmol) and thionyl chloride (0.80 mL, 1.30 g, 11.0 mmol) was stirred under reflux for 14 h, and then

cooled to room temperature. The mixture was transferred to a small flask and the reaction vessel was rinsed with carbon tetrachloride (ca. 1 mL). The solvent and excess of reagent were evaporated to give acid chloride **156** (191.5 mg, 97%) as a brown solid: IR (CCl_4) 2960, 2940, 2840, 1790, 1460, 1430, 1410, 1300, 1260, 1190, 1175, 1145, 1075, 1035, 940, 700, 675 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ6.93 (d, J = 9.0 Hz, 1H), 6.85 (d, J = 9.0 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ167.7, 152.6, 149.5, 135.6, 112.7, 112.6, 82.6, [illegible] 56.9; exact mass, m/z 327.9180 (calcd for $C_9H_8O_3{}^{37}Cl$, m/z 327.9177) and 325.9207 (calcd for $C_9H_8O_3{}^{35}Cl$, m/z 325.9207).

Attempted preparation of **83**

Ester **70** (42.6 mg, 0.2065 mmol) in THF (1.0 mL plus 2 × 0.5 mL rinse) was added dropwise over ca. 2 min, to a cold (-78°C) solution of LDA (0.35 mL, 0.71 M stock solution, 0.248 mmol) under argon. The solution was stirred at -78°C for 45 min and acid chloride **156** (79.7 mg, 0.244 mmol) in THF (1.0 mL plus 1.0 mL rinse) was then injected quickly. The mixture was stirred at -78°C for 10 min, at 0°C for 30 min, and then cooled to -78°C. LDA (0.35 mL, 0.71 M stock solution, 0.248 mmol) was added and the mixture was slowly warmed to room temperature

overnight. Saturated aqueous ammonium chloride (ca. 2 mL) and water (ca. 8 mL) were added and the mixture was extracted with dichloromethane (2 × ca. 15 mL). The combined extracts were washed with brine (1 × ca. 10 mL), dried, and evaporated. Analysis of the crude residue [TLC (silica, 3:1 hexane – ethyl acetate) and ^1H NMR ($CDCl_3$, 400 MHz)] showed a complex mixture of compounds.

2,3-Dihydro-1-[hydroxy(3,6-dimethoxy-2-iodophenyl)-methylene]-7-methoxy-1H-indene (**160**)

Acid chloride **156** (191.5 mg, 0.5864 mmol) in THF (1.0 mL plus 1.0 mL rinse) was added to a cold (-78°C) solution of dianion **71** {2.43 mL, 0.216 M stock solution, [prepared from n-butyllithium (0.83 mL, 1.55 M in hexane, 1.284 mmol) and acid **65** (117.5 mg, 0.6112 mmol) in THF (2.0 mL) at 0°C] 0.525 mmol) under argon. The mixture was stirred at -78°C for 10 min and at 0°C for 1 h. Saturated aqueous ammonium chloride (ca. 3 mL) was added and stirring was continued at room temperature for 1 h. Water was added (ca. 10 mL) and the mixture was extracted with ether (2 × ca. 20 mL). The aqueous layer was acidified to pH 1 by addition of dilute hydrochloric acid and back-extracted with dichloromethane (2 × ca. 20 mL). The combined dichloromethane extracts were dried and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm)

with 6:1 hexane – ethyl acetate gave **160** (62.3 mg, 27%) as a slightly impure (TLC) sample. (Attempts to further purify **160** by preparative thin layer chromatography were unsuccessful): IR (CCl_4) 3410, 2960, 2940, 2910, 2840, 1735, 1705, 1658, 1465, 1430, 1310, 1260, 1065, 1035 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.22 (s, 1H), 7.13 (t, J = 7.5 Hz, 1H), 6.91 (d, J = 8.5 Hz, 2H), 6.78 (m, 2H), 4.02 (s, 3H), 3.86 (s, 3H), 3.79 (s, 3H), 2.85 (m, 2H), 2.36 (m, 1H), 2.26 (m, 1H); exact mass, m/z 438.0325 (calcd for $C_{19}H_{19}O_4I$, m/z 438.0328).

The combined ether extracts were washed with brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm) with 6:1 hexane – ethyl acetate gave an apparently homogeneous (R_f = 0.18; TLC, silica, 5:1 hexane – ethyl acetate) residue (17.9 mg). The ^1H NMR ($CDCl_3$, 400 MHz) showed the presence of enol **160** along with at least two other unidentified compounds.

Preparation of **140** from 3,6-dimethoxy-2-iodobenzaldehyde dimethyl acetal (**161**)

Amberlite IR-120 ion exchange resin* (5 mg) was added

*Washed successively with methanol and ether, and dried at 140°C overnight.

to a solution of aldehyde **139** (18.6 mg, 0.0636 mmol) and trimethyl orthoformate (0.10 mL, 97 mg, 0.914 mmol) in methanol (1.0 mL). The mixture was stirred at room temperature for 7 h and filtered. The resin was washed with ether (ca. 2 mL) and the combined filtrates were evaporated. The crude residue was dried under oil-pump vacuum for 2 h (17.8 mg). The ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of the residue showed the presence of both the desired dimethyl acetal **161** [δ6.92 (d, J = 9.0 Hz, 0.85H), 6.79 (d, J = 9.0 Hz, 0.85H), 5.81 (s, 0.73H), 3.833 (s), 3.829 (s), 3.48 (s, 5.0H). The signals at δ3.833 and δ3.829 together have an area which corresponds to 6.0H], and the unreacted aldehyde **139** [δ7.00 (d, J = 9.0 Hz, 0.15 H), 6.96 (d, J = 9.0 Hz, 0.15H), 3.874 (s), 3.870 (s). The signals at δ3.874 and δ3.870 together have an area which corresponds to 0.24H] in a ratio of ca. 6:1.

A mixture of impure acetal **161** (17.8 mg) and phenyl copper(I) acetylide (23.1 mg, 0.1404 mmol) in pyridine[79] (1.0 mL) was stirred and reflux under argon for 12 h. The mixture was cooled to room temperature and dilute hydrochloric acid (15 mL, 1 M) was added. This mixture was then extracted with ether (2 × 20 mL) and the combined extracts were washed with dilute hydrochloric acid (2 × 10 mL, 1 M) and brine (1 × 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1 ×

17 cm) with 2:1 hexane – ethyl acetate allowed separation of the mixed fractions of dimethyl acetal **162** (R_f = 0.27, TLC, silica, 2:1 hexane – ethyl acetate) and aldehyde **140** (R_f = 0.31) from phenylacetylene (R_f = 0.87).

Hydrolysis of the acetal was completed by addition of 10% aqueous oxalic acid (1.0 mL) to a dioxane (1.0 mL) solution of the mixed fractions. The mixture was stirred at room temperature for 3 h, diluted with water (ca. 10 mL), and extracted with ether (2 × 15 mL). The combined extracts were washed with 5% aqueous sodium bicarbonate (1 × ca. 10 mL) and brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) with 2:1 hexane – ethyl acetate followed by CHROMATOTRON purification using 2:1 hexane – ethyl acetate and silica, gave **140** (9.3 mg, 55% overall yield).

2,3-Dihydro-7-methoxy-1-[hydroxy[3,6-dimethoxy-2-(phenylethynyl)phenyl]methyl]-1H-indene-1-carboxylic acid (**163**)

Acid **65** (45.1 mg, 0.2346 mmol) in THF (1.0 mL plus 2 × 0.5 mL rinse) was added dropwise over ca. 2 min to a cold (-78°C) solution of LDA (0.79 mL, 0.71 M stock solution, 0.561 mmol) under argon. The solution was stirred at -78°C for 1 h and at 50°C for 1 h, and then cooled to -78°C. Aldehyde **140** (71.1 mg, 0.2669 mmol) in

THF (1.0 mL plus 2 × 0.5 mL rinse) was injected quickly. The mixture was stirred at -78°C for 1 h and at room temperature for 30 min. It was then quenhed by addition of saturated aqueous ammonium chloride (ca. 5 mL) and dilute hydrochloric acid (ca. 15 mL, 1 M). The mixture was extracted with dichloromethane (2 × ca. 40 mL) and the combined extracts were dried and evaporated. Ethyl acetate (ca. 10 mL) and methanol (3 drops) were added, and β-hydroxyacid **163** (31.4 mg, 29.2%) was collected as an insoluble pale yellow solid: mp 233-240°C; IR (nujol) 3550, 1685, 1480, 1440, 1265, 1248, 1080, 1070, 1052, 810, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) showed the presence of only one of the two possible diastereoisomers of **163**: δ7.52 (m, 2H), 7.35 (m, 3H), 7.13 (t, J = 7.5 Hz, 1H), 6.77 (d, J = 9.0 Hz, 1H), 6.73 (d, J = 8.0 Hz, 1H), 6.66 (d, J = 7.5 Hz, 1H), 6.62 (d, J = 9.0 Hz, 1H), 5.96 (d, J = 11.5 Hz, 1H), 5.23 (d, J = 12.0 Hz, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.20 (s, 3H), 2.90 (ddd, J = 0.5, 7.5, 13.0 Hz, 1H), 2.78 – 2.58 (m, 2H), 1.97 (m, 1H). Upon D_2O exchange the signal at δ5.23 disappeared and the signal at δ5.96 collapsed to a singlet. Exact mass, m/z 458.1739 (calcd for $C_{28}H_{26}O_6$, m/z 458.1730). Treatment of acid **163** with an excess of diazomethane gave the corresponding β-hydroxyester whose ^1H NMR ($CDCl_3$, 400 MHz) spectrum proved to be identical with that of an authentic sample of the

lower R_f isomer of **165**.

The ethyl acetate-methanol filtrate was evaporated and flash chromatography of the residue over silica gel (2 × 15 cm) with 1:1 hexane – ethyl acetate allowed recovery of aldehyde **140** (25.4 mg) as a slightly impure (TLC) sample. Several polar mixed fractions were also collected; however, the ^{1}H NMR (400 MHz) spectra of these mixed fractions were not consistent with the presence of the desired β-hydroxyacids and no further work was carried out on these samples.

Attempted oxidation of **163**

a) A mixture of β-hydroxyacid **163** (8.8 mg, 0.0191 mmol) and pyridinium chlorochromate (29.5 mg, 0.137 mmol) in dichloromethane (1.5 mL) was stirred at room temperature under argon for 7 h. Dilute hydrochloric acid (*ca.* 3 mL, 1 *M*) was added and stirring was continued for 1 h. Additional dilute hydrochloric acid (*ca.* 5 mL, 1 *M*) was added and the mixture was extracted with ether (2 × *ca.* 20 mL). The combined extracts were washed with brine (1 × *ca.* 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) with 1:1 hexane – ethyl acetate gave aldehyde **140** (1.3 mg, 25%) as the only major reaction component.

b) A mixture of β-hydroxyacid **163** (6.4 mg, 0.0139

mmol) and manganese dioxide (52.6 mg, 0.605 mmol) in chloroform (1.5 mL) was stirred at room temperature under argon for 18 h. Glacial acetic acid (3 drops) was added and stirring was continued for 1.5 h. The insoluble material was filtered off and washed with dichloromethane (ca. 5 mL). Water (ca. 10 mL) was added to the combined filtrates and the aqueous layer was extracted with dichloromethane (2 × ca. 10 mL). The combined organic extracts were dried and evaporated. The ^{1}H NMR (400 MHz) spectrum of the crude residue showed only the presence of unreacted starting material.

Methyl 2,3-dihydro-7-methoxy-1-[hydroxy[3,6-dimethoxy-2-(phenylethynyl)phenyl]methyl]-1H-indene-1-carboxylate (**165**)

Ester **70** (45.1 mg, 0.2186 mmol) in THF (1.0 mL plus 1.0 mL rinse) was added dropwise over ca. 2 min to a cold (-78°C) solution of LDA (0.46 mL, 0.71 M stock solution, 0.32 mmol) under argon. The solution was stirred at -78°C for 50 min. Aldehyde **140** (63.6 mg, 0.2388 mmol) in THF (1.0 mL plus 1.0 mL rinse) was injected quickly. The mixture was stirred at -78°C for 1.25 h and then at room temperature for 10 min. It was then quenched by addition of saturated aqueous ammonium chloride (ca. 5 mL) and water (ca. 10 mL). The mixture was extracted with

dichloromethane (2 × ca. 20 mL) and the combined extracts were washed with brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm) with 3:1 hexane – ethyl acetate, followed by 1:1 hexane – ethyl acetate, allowed partial separation of the diastereoisomers of **165** (56.6 mg, 54.8%): lower R_f isomer (13.7 mg) (R_f = 0.24; TLC, silica, 1:1 hexane – ethyl acetate): FTIR (CH_2Cl_2, cast) 3550, 1711.7, 1482.4, 1442.6, 1266.1, 1247.4, 1080.9, 1070.5 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ7.65 (dd, J = 2.0, 7.5 Hz, 2H), 7.36 (m, 3H), 7.15 (t, J = 7.5 Hz, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.72 (d, J = 9.0 Hz, 1H), 6.66 (d, J = 7.5 Hz, 1H), 6.53 (d, J = 9.0 Hz, 1H), 6.49 (d, J = 11.0 Hz, 1H), 4.56 (d, J = 11.0 Hz, 1H), 3.87 (s), 3.86 (s), 3.78 (s, 3H), 3.07 (s, 3H), 2.89 (ddd, J = 1.0, 8.0, 13.0 Hz, 1H), 2.50 (dd, J = 9.0, 15.5 Hz, 1H), 2.15 (m, 1H), 1.83 (m, 1H). Upon D_2O exchange, the signal at δ4.56 disappeared and the signal at δ6.49 collapsed to a singlet. Exact mass, m/z 472.1890 (calcd for $C_{29}H_{28}O_6$, m/z 472.1886).

Mixture of diastereoisomers (R_f = 0.36; R_f = 0.24) (42.9 mg): The ^1H NMR spectrum showed the presence of two diastereoisomers in a ratio of ca. 1:3 (high R_f:low R_f). ^1H NMR ($CDCl_3$, 200 MHz) δ7.65 (m, 1.7H), 7.36 (m, 2.8H), 7.16 (t, J = 7.5 Hz), 7.12 (t, J = 7.5 Hz), 6.84 – 6.60 (m

containing doublets at δ6.79 (d, J = 7.5 Hz) and δ6.72 (d, J = 9.0 Hz), 3.4H], 6.55 (d, J = 9.0 Hz), 6.51 (11.0 Hz), 6.23 (d, J = 5.5 Hz, 0.25H), 4.96 (d, J = 5.5 Hz, 0.25H), 4.57 (d, J = 11.0 Hz, 0.82H), 3.87 (s), 3.86 (s), 3.82 (s, 0.82H), 3.78 (s, 2.2H), 3.70 (s), 3.69 (s), 3.07 (s, 2.3H), 2.93 (m, 0.95H), 2.84 – 2.44 (m, 1.2H), 2.22 (m, 1.1H), 1.88 (m, 0.63H). The signals at δ7.16 and 7.12 together have an area which corresponds to 1.0H, those at δ6.55 and 6.51 to 1.55H, those at δ3.87 and 3.86 to 4.6H, and those at δ3.70 and 3.69 to 0.57H. Upon D_2O exchange the signals at δ4.96 and δ4.57 disappeared and the signals at δ6.23 and δ6.51 collapsed to singlets. Irradiation at δ6.57 collapsed the doublet at δ6.51 to a singlet.

Methyl 2,3-dihydro-1-[3,6-dimethoxy-2-(phenylethynyl)-benzoyl]-7-methoxy-1H-indene-1-carboxylate (**166**)

A mixture of β-hydroxyester **165** (14.6 mg, 0.0308 mmol) and pyridinium chlorochromate (36.5 mg, 0.169 mmol) in dichloromethane (1.5 mL) was stirred at room temperature under argon for 18 h. Dilute hydrochloric acid (ca. 10 mL, 1 M) was added and the mixture was extracted with dichloromethane (2 × ca. 20 mL). The combined extracts were washed with brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) with 1:1 hexane –

ethyl acetate allowed separation of unreacted starting material **165** (7.3 mg, 50% recovery) from β-ketoester **166** (4.4 mg, 30%). The latter had: IR (nujol) 1730, 1695, 1260 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ7.51 (m, 2H), 7.30 (m, 3H), 7.17 (t, J = 7.8 Hz, 1H), 6.82 (d, J = 8.5 Hz), 6.81 (d, J = 7.5 Hz), 6.63 (d, J = 9.0 Hz, 1H), 6.54 (d, J = 7.5 Hz, 1H), 3.86 (s, 3H), 3.53 (s, 3H), 3.51 (s, 3H), 3.46 (s, 3H), 3.00 (m, 3H), 2.78 (m, 1H). The signals at δ6.82 and δ6.81 together have an area which corresponds to 2H. ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ171.7, 156.8, 154.6, 150.2, 147.8, 131.9, 130.0, 129.0, 128.13, 128.08, 126.8, 116.6, 112.5, 110.6, 108.7, 97.3, 83.6, 71.4, 56.9, 55.5, 55.1, 52.1, 37.7, 31.9;* exact mass, m/z 470.1727 (calcd for $C_{29}H_{26}O_6$, m/z 470.1729).

1-Methoxy-3-methyl-2-nitrobenzene (**171**)

Anhydrous potassium carbonate (94.5 g, 684 mmol) was added to a solution of 2-nitro-3-hydroxytoluene** **170** (36.2 g, 236 mmol) and dimethyl sulfate (50 mL, 66.7 g, 528 mmol) in acetone (250 mL, reagent grade). The mixture

*Not all of the carbon signals were resolved in this spectrum.

**Prepared by Dr. D.L.J. Clive according to the procedure of reference 94.

was stirred under reflux for 24 h, cooled to room temperature, and filtered. The solid was washed with acetone (ca. 150 mL) and the combined filtrates were diluted with dichloromethane (ca. 400 mL), washed with water (ca. 400 mL) and brine (ca. 400 mL), dried, and evaporated to give **171** as a pale yellow oil (36.65 g, 93%). A portion was recrystallized from 95% ethanol to give white crystals: mp 45-51°C (lit.[91] 52-53°C); IR (film) 1608, 1580, 1520, 1475, 1455, 1438, 1365, 1282, 1085, 1070, 850, 775 cm^{-1}; ^1H NMR [acetone-d_6 (1% D_2O), 200 MHz] δ7.38 (t, J = 8.0 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 3.87 (s, 3H), 2.94 (s, 3H); ^{13}C NMR (acetone-d_6, 50.32 MHz) δ151.9, 132.1, 131.5, 123.7, 111.7, 57.2, 17.0; exact mass, m/z 167.0581 (calcd for $C_8H_9O_3N$, m/z 167.0583).

3-Methoxy-2-nitrobenzoic acid (**172**)

The procedure of reference 94 was used to prepare **172**: 3-methoxy-2-nitrotoluene **171** (3.10 g, 18.5 mmol), potassium permanganate (8.2 g, 51.9 mmol) and water (325 mL) were stirred under reflux for 24 h. The mixture was cooled to room temperature, made basic with aqueous sodium hydroxide (ca. 150 mL, 6 M) and extracted with ether (2 × ca. 200 mL). The aqueous layer was filtered to remove manganese dioxide and the filtrate was acidified, to pH 1,

with concentrated hydrochloric acid, and cooled to 0°C. The white precipitated acid **172** was collected and dried (2.30 g, 63%): IR (nujol) 1685, 1575, 1535, 1435, 1295, 1275, 1050 cm^{-1}; ^1H NMR [acetone-d_6 (1% D_2O), 200 MHz] δ7.60 (m, 2H), 7.44 (dd, J = 2.0, 7.5 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR (acetone-d_6, 100.61 MHz) δ164.3, 151.8, 131.9, 124.8, 122.9, 118.5, 57.4; exact mass, m/z 197.0326 (calcd for $C_8H_7O_5N$, m/z 197.0324).

3-Hydroxy-2-nitrobenzoic acid (**173**)

The general procedure of reference 91, with some modifications, was used to prepare **173**: a mixture of 3-methoxy-2-nitrobenzoic acid (3.94 g, 20.0 mmol) and pyridine hydrochloride (16.2 g, 140 mmol) was heated at 180-200°C for 12 h and then cooled to room temperature. Aqueous sodium hydroxide (ca. 300 mL, 1 M) was added and the mixture was extracted with ether (2 × ca. 150 mL). The aqueous layer was acidified to pH 1 and back-extracted with ether (3 × ca. 200 mL). The combined extracts were dried and evaporated. Recrystallization from water gave **173** (3.23 g, 78%) as yellow crystals: mp 159-166°C (lit.[91] 178-180°C); IR (nujol) 1690, 1610, 1520, 1330 cm^{-1}; ^1H NMR [acetone-d_6 (1% D_2O), 400 MHz] δ7.51 (d, J = 7.5 Hz), 7.50 (s), 7.48 (d, J = 7.5 Hz), 7.38 (m, 1H). The signals at δ7.51, 7.50 and 7.48 together have an area

which corresponds to 2.5H. (Presumably some exchange of the hydroxyl proton with D_2O present in the solvent is occurring.) ^{13}C NMR (acetone-d_6, 100.61 MHz) δ164.8, 150.2, 131.8, 125.7, 122.5, 122.0; exact mass, m/z 183.0168 (calcd for $C_7H_5O_5N$, m/z 183.0168).

Benzyl 3-benzyloxy-2-nitrobenzoate (**174**) and 3-benzyloxy-2-nitrobenzoic acid (**175**)

The procedure of reference 95 was used to prepare **175**: 3-hydroxy-2-nitrobenzoic acid (433.8 mg, 2.37 mmol) in ethanol (2.0 mL plus 1.0 mL rinse) was added to a freshly prepared solution of sodium ethoxide in ethanol [prepared from sodium (143 mg, 6.22 mmol) and absolute ethanol (4.0 mL)]. The mixture was stirred under reflux, under argon for 75 min and benzyl chloride (1.40 mL, 1.54 g, 12.2 mmol) was then added. Stirring under reflux was continued for 36 h. The mixture was cooled to room temperature, acidified by addition of dilute hydrochloric acid (ca. 50 mL, 1 M), and extracted with ether (2 × ca. 50 mL). The combined extracts were dried and evaporated. Flash chromatography of the residue over silica gel allowed separation of benzyl 3-hydroxy-2-nitrobenzoate (197 mg, 30%) and unreacted starting material (not isolated) from benzyl 3-benzyloxy-2-nitrobenzoate **174** (297.3 mg, 34.5%). The latter had: mp 70-80°C; IR (CCl_4)

1730, 1470, 1445, 1365, 1285, 1185, 1160, 1120, 1050, 1025, 695 cm^{-1}; ^1H NMR [acetone-d_6 (1% D_2O), 400 MHz] δ7.63 (m, 3H), 7.49 – 7.30 (m, 10H), 5.34 (s, 4H); exact mass, m/z 363.1080 (calcd for $C_{21}H_{17}O_5N$, m/z 363.1107).

A mixture of benzyl ester **174** (840.9 mg, 2.314 mmol) and potassium hydroxide (550 mg, 9.80 mmol) in ethanol (6.0 mL, 98%) was stirred under reflux for 2.5 h, cooled to room temperature, diluted with water (ca. 30 mL), and extracted with ether (2 × ca. 30 mL) and the combined ether extracts were washed with aqueous sodium hydroxide (1 × ca. 30 mL, 1.2 M). The combined aqueous extracts were acidified to pH 1 and back-extracted with ether (2 × ca. 100 mL). These combined ether extracts were dried and evaporated. Recrystallization of the residue from 98% ethanol gave **175** (569.1 mg, 90%) as a pale yellow solid: mp 198-203°C (lit.[95] 192-193°C); IR (nujol) 1680, 1575, 1535, 1305, 760 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ7.64 (m, 3H), 7.48 – 7.31 (m, 5H), 5.34 (s, 2H); exact mass, m/z 167.0217 [calcd for $C_7H_5O_4N$ ($M-C_7H_6O$), m/z 167.0219] and 91.0531 [calcd for C_7H_7 ($M-C_7H_4O_5N$), m/z 91.0548].

2-Amino-3-benzyloxybenzoic acid (**176**)

The procedure of reference 91 was used to prepare **176**: sodium dithionite (9.1 g, 52.3 mmol) in water (50 mL) was added dropwise over 20 min to a solution of nitro-

acid **175** (1.4156 g, 5.18 mmol) in aqueous sodium hydroxide (25 mL, 2 M). The mixture was then stirred under reflux for 12 h and cooled to room temperature. The solution was carefully neutralized to pH 7 by addition of dilute hydrochloric acid (1 M) and extracted with ether (2 × ca. 100 mL). The combined extracts were dried and evaporated to leave **176** (993 mg, 78.8%) as a pale yellow solid: mp 165-170°C (lit.[91] 173-175°C); IR (nujol) 3500, 3375, 1665, 1315, 1278, 1245, 1220, 1210, 1025, 745, 740, 700 cm^{-1}; ^1H NMR [acetone-d_6 (1% D_2O), 200 MHz] δ7.58 – 7.25 (m, 6H), 7.05 (dd, J = 1.5, 8.0 Hz, 1H), 6.52 (t, J = 8.0 Hz, 1H), 5.16 (s, 2H); exact mass, m/z 243.0894 (calcd for $C_{14}H_{13}O_3N$, m/z 243.0896).

Methyl 3-benzyloxy-2-iodobenzoate (**177**)

The procedure of reference 91 was used to prepare 3-benzyloxy-2-iodobenzoic acid: sodium nitrite (95 mg, 1.38 mmol) in water (1.0 mL) was added over ca. 30 min to a cold (0°C) solution of 2-amino-3-benzyloxybenzoic acid[91] (293 mg, 1.204 mmol) in acidic methanol [conc H_2SO_4 (530 mg) in MeOH (8 mL)]. The mixture was stirred at 0°C for a further 30 min and a cold (0°C) aqueous solution of potassium iodide [1.12 g, 6.75 mmol in H_2O (8 mL)] was added. Stirring was then continued overnight. Dilute hydrochloric acid (ca. 50 mL, 1 M) was added and the

mixture was extracted with ether (2 × ca. 50 mL). The combined extracts were dried, dissolved in ether (ca. 20 mL) and cooled to 0°C. An excess of ethereal diazomethane was added and the excess was destroyed by addition of silica gel. The mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm) with 20:1 hexane – ethyl acetate gave methyl 3-benzyloxy-2-iodobenzoate (250.4 mg, 56.5%) as a yellow oil: IR (film) 1720, 1560, 1430, 1295, 1265, 1045, 1025, 758, 738, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ7.51 (d, J = 7.5 Hz, 2H), 7.40 (dt, J = 1.0, 7.5 Hz, 2H), 7.37 – 7.23 (m, 4H), 6.95 (dd, J = 1.5, 8.0 Hz, 1H), 5.19 (s, 2H), 3.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ167.9, 158.1, 136.3, 129.1, 128.6, 128.1, 127.2, 122.8, 115.1, 87.6, 71.7, 52.4; mass spectrum (CI), m/z 386 (M+18). Anal. calcd for $C_{15}H_{13}O_3I$: C, 48.94; H, 3.56; O, 13.07. Found: C, 49.28; H, 3.58; O, 13.27.

Methyl 3-benzyloxy-2-(phenylethynyl)benzoate (**178**)

Pyridine (6.0 mL) was added to a mixture of copper(I) phenylacetylide[79] (266.9 mg, 1.62 mmol) and iodoester **177** (229.4 mg, 0.623 mmol) under argon. The mixture was stirred under reflux for 15 h, cooled to room temperature, diluted with hydrochloric acid (50 mL, 1 M), and extracted with ether (2 × 50 mL). The combined extracts were washed

with dilute hydrochloric acid (1 × 50 mL, 1 M) and brine (1 × 50 mL), dried, and evaporated. Flash chromatography of the residue twice over silica gel (2 × 15 cm) with 5:1 hexane – ethyl acetate gave **178** (191.9 mg, 90%) as a yellow oil. Kugelrohr distillation provided an analytical sample: bp 147°C (0.025 mm); FTIR (CCl_4, cast) 1729.0, 1450.0, 1304.9, 1270.2, 1054.5, 755.7, 692.1 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ7.53 (m, 5H), 7.34 (m, 7H), 7.09 (d, J = 8.0 Hz, 1H), 5.17 (s, 2H), 3.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ166.9, 160.3, 136.9, 134.1, 131.8, 128.8, 128.6, 128.3, 128.0, 127.1, 124.0, 122.9, 116.4, 114.3, 99.6, 84.2, 71.3, 52.1; exact mass, m/z 342.1257 (calcd for $C_{23}H_{18}O_3$, m/z 342.1257). Anal. calcd for $C_{23}H_{18}O_3$: C, 80.68; H, 5.30. Found: C, 80.41; H, 5.43.

3-Benzyloxy-2-(phenylethynyl)benzoic acid (**179**)

Ester **178** (18.2 mg, 0.0531 mmol) in THF (1.0 mL plus 0.7 mL rinse) was added to a mixture of potassium t-butoxide (55.7 mg, 0.497 mmol) and water (3.0 μL, 3.0 mg, 0.166 mmol) under argon.[84] The mixture was stirred under reflux for 20 h, cooled to room temperature, diluted with water (ca. 5 mL) and extracted with ether (2 × ca. 10 mL). The combined extracts were washed with aqueous sodium hydroxide (ca. 10 mL, 1 M). The combined basic aqueous layers were acidified to pH 1 by addition of

dilute hydrochloric acid, and back-extracted with ether (1 × 15 mL). The organic extract was dried and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) with 1:1 hexane – ethyl acetate gave **179** (6.1 mg, 35%) as a white solid: mp 120-130°C; FTIR ($CHCl_3$, cast) 1695.1, 1301.7, 1289.2, 1271.2, 754.3 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ7.75 (dd, J = 1.0, 8.0 Hz, 1H), 7.56 (m, 4H), 7.44 – 7.28 (m, 7H), 7.19 (dd, J = 0.5, 9.0 Hz, 1H), 5.24 (s, 2H); exact mass, m/z 328.1100 (calcd for $C_{22}H_{16}O_3$, m/z 328.1100). Treatment of acid **179** with diazomethane gave a compound whose ^1H NMR ($CDCl_3$, 400 MHz) spectrum proved to be identical with that of the starting material.

1-[3-Benzyloxy-2-(phenylethynyl)benzoyl]-2,3-dihydro-7-methoxy-1H-indene (**180**)

n-Butyllithium (0.25 mL, 1.31 M in hexane, 0.33 mmol) was added dropwise over ca. 2 min to a cold (0°C) solution of acid **65** (30.1 mg, 0.1565 mmol) in THF (1.5 mL) under argon. The mixture was stirred at 0°C for 1 h. HMPA (0.23 mL, 1.44 mM in THF, 0.33 mmol) was added. Stirring was continued at 0°C for 30 min and ester **178** (75.3 mg, 0.2199 mmol) in THF (1.0 mL plus 2 × 0.5 mL rinse) was then injected quickly. The solution was stirred at 0°C for 30 min and at 50°C for 2 h. The reaction mixture was cooled to room temperature and quenched with saturated

aqueous ammonium chloride (ca. 4 mL). Water (ca. 10 mL) and ether (ca. 10 mL) were added and stirring was continued at room temperature for 12 h. Dilute hydrochloric acid (ca. 10 mL, 1 M) was added and the aqueous layer was extracted with ether (2 × ca. 20 mL). The combined extracts were washed with 10% aqueous copper sulfate (2 × ca. 20 mL) and brine (1 × ca. 20 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm) with 8:1 hexane – ethyl acetate allowed separation of unreacted starting material **178** (34.1 mg, 45.3% recovery) from the product **180** (36.4 mg, 50.7%). Recrystallization from ethyl acetate – hexane provided an analytical sample: mp 97-103°C; FTIR (CH_2Cl_2, cast) 1692, 1590, 1480, 1450, 1308, 1292, 1266.2, 1075, 755, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ7.54 (d, J = 7.0 Hz, 2H), 7.45 (m, 2H), 7.37 (t, J = 7.0 Hz, 2H), 7.30 (m, 5H), 7.22 (d, J = 7.5 Hz, 1H), 7.17 (t, J = 7.5 Hz, 1H), 7.04 (d, J = 7.5 Hz, 1H), 6.87 (d, J = 7.5 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 5.25 (dd, J = 5.0, 8.0 Hz, 1H), 5.19 (s, 2H), 3.58 (s, 3H), 3.16 (m, 1H), 2.94 (m, 1H), 2.49 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ204.8, 159.9, 156.1, 146.9, 144.7, 137.0, 131.6, 130.6, 129.0, 128.7, 128.5, 128.2, 127.9, 127.1, 123.7, 120.8, 117.1, 114.9, 111.8, 108.3, 99.1, 84.4, 71.2, 55.0, 53.8, 32.6, 30.6; exact mass, m/z 458.1885 (calcd for $C_{32}H_{26}O_3$, m/z 458.1882).

Anal. calcd for $C_{32}H_{26}O_3$: C, 83.82; H, 5.715. Found: C, 83.57; H, 5.88.

1-[3-Benzyloxy-2-(phenylethynyl)benzoyl]-2,3-dihydro-7-methoxy-1-(phenylseleno)-1H-indene (**181**)

Ketone **180** (46.0 mg, 0.1003 mmol) in THF (1.0 mL plus 2 × 0.5 mL rinse) was added dropwise over ca. 2 min to a cold (-78°C) solution of LDA (0.24 mL, 0.62 M stock solution, 0.149 mmol) under argon. The mixture was stirred at -78°C for 1.2 h and phenylselenenyl chloride (48.6 mg, 0.254 mmol) in THF (0.70 mL) was added. Stirring was continued at -78°C for 1.5 h and then at 0°C for 20 min. Saturated aqueous ammonium chloride (2 mL) and water (ca. 10 mL) were added and the mixture was extracted with ether (2 × ca. 15 mL). The combined extracts were washed with brine (1 × ca. 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm) with 8:1 hexane – ethyl acetate gave **181** (49.8 mg, 81%). Recrystallization from ethyl acetate provided an analytical sample: mp 140-143°C; FTIR (CCl_4, cast) 1697.1 (shoulder at 1680), 1588.1, 1567.8, 1492.7, 1479.3, 1464.4, 1449.1, 1292.9, 1268.6, 1082.5, 1068.6, 785.3, 757.3, 741.2, 692.8 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ7.51 (m, 4H), 7.34 (m, 8H), 7.25 (t, J = 7.0 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 7.08 (dt, J = 1.0, 8.0 Hz,

3H), 6.91 (d, J = 8.0 Hz, 1H), 6.87 (d, J = 7.5 Hz, 1H), 6.60 (dd, J = 7.5, 3.0 Hz, 2H), 5.17 (s, 2H), 3.61 (s, 3H), 2.94 (m, 1H), 2.66 (m, 2H), 2.27 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ201.8, 159.2, 155.9, 146.7, 144.0, 138.0, 136.9, 131.8, 131.0, 130.2, 128.52, 128.49, 128.24, 128.19, 127.9, 127.0, 123.7, 119.6, 117.1, 113.7, 111.9, 108.7, 97.9, 84.1, 70.9, 69.0, 55.1, 39.6, 31.8; exact mass, m/z 614.1365 (calcd for $C_{38}H_{30}O_3{}^{80}Se$, m/z 614.1360). Anal. calcd for $C_{38}H_{30}O_3Se$: C, 74.38; H, 4.93. Found: C, 74.05; H. 4.99.

2,3-Dihydro-7-methoxy-1H-indene-1-spiro4'-[3',3a'-dihydro-2',3'-diphenyl]cyclopenta[4,3,2-d,e]benzo-[2H]-pyran-5'-one (**187**)

a) A refluxing solution (4.0 mL) of ketone **181** (49.8 mg, 0.0811 mmol) in benzene was maintained under a slight static pressure of argon. AIBN (2.8 mg, 0.017 mmol) in benzene (2.0 mL) and triphenyltin hydride (41.1 mg, 0.117 mmol) in benzene (2.0 mL) were added simultaneously over 7 h (syringe pump).[32] Refluxing was continued for 12 h and the solvent was then evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm) with 8;1 hexane – ethyl acetate allowed isolation of two diastereoisomers of **187**. The isomer with lower R_f (R_f = 0.36; TLC, silica, 5:1 hexane – ethyl acetate) was the major product (18.4

mg, 49.6%). Recrystallization from ether – ethyl acetate provided an analytical sample: mp 246-248°C with decomposition noted at 230°C; FTIR (CH_2Cl_2, cast) 1718.5, 1605.7, 1590.7, 1478.8, 1454.9, 1263.7, 1080.7, 763.4, 738.7, 698.5 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ7.41 (m, 2H), 7.16 (m, 4H), 7.04 (m, 3H), 6.93 (t, J = 7.5 Hz, 1H), 6.80 (t, J = 7.5 Hz, 2H), 6.66 (d, J = 8.0 Hz, 1H), 6.53 (d, br ($W_{1/2}$ = 16 Hz), J = 6.0 Hz, 2H), 6.41 (d, J = 7.5 Hz, 1H), 5.24 (d, J = 10.0 Hz, 1H), 4.49 (d, J = 12.0 Hz, 1H), 3.76 (s, 3H), 3.19 (dd, J = 10.0, 12.0 Hz, 1H), 2.56 (ddd, J = 2.5, 9.0, 11.5 Hz, 1H), 2.02 (m, 2H), 1.72 (m, 1H). Irradiation at δ6.53 simplified the signals at δ7.04 and δ6.80, and irradiation at either δ5.24 or δ4.49 simplified the signal at δ3.19. ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ208.3 (s), 155.1 (s), 153.4 (s), 147.1 (s), 139.1 (s), 138.8 (s), 137.3 (s), 136.0 (s), 133.0 (s), 129.6 (d), 129.2 (d), 128.1 (d), 128.0 (d), 127.7 (d), 127.3 (d), 126.8 (d), 119.3 (d), 116.9 (d), 115.8 (d), 108.3 (d), 86.1 (d), 66.7 (s), 55.5 (q), 47.9 (d), 46.2 (d), 32.4 (t), 31.9 (t); exact mass, m/z 458.1873 (calcd for $C_{32}H_{26}O_3$, m/z 458.1882), 278.0942 (calcd for $C_{18}H_{14}O_3$ (M-$C_{14}H_{12}$), m/z 278.0942). Anal. calcd for $C_{32}H_{26}O_3$: C, 83.82; H, 5.715. Found: C, 83.43; H, 5.69.

The isomer with the higher R_f (R_f = 0.42, 4.6 mg, 12.4%) contained trace impurities (TLC) and had: FTIR

(CH_2Cl_2, cast) 1720.0, 1606.2, 1587.2, 1498.7, 1477.1, 1450.2, 1267.5, 1110.6, 1083.0, 1045.2, 1032.5, 792.1, 758.9, 746.5, 698.0 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ7.38 (m, 10H), 6.92 (t, J = 7.0 Hz, 1H), 6.76 (t, J = 7.5 Hz, 2H), 6.68 (d, J = 7.0 Hz, 2H), 5.62 (d, J = 8.0 Hz, 1H), 5.46 (br s, 1H), 3.56 (d, J = 5.5 Hz, 1H), 3.39 (dd, J = 1.0, 6.0 Hz, 1H), 3.01 (ddd, J = 6.0, 9.0, 9.5 Hz, 1H), 2.84 (s), 2.85 (dd, J = 9.0, 15.0 Hz), 2.69 (m, 1H), 1.88 (dd, J = 6.0, 12.0 Hz, 1H). The signals at δ2.84 and δ2.85 together have an area which corresponds to 4H. Irradiation at δ5.62 resulted in simplification of the signal at δ6.76. Irradiation at δ3.39 resulted in collapse of the doublet at δ3.56 to a singlet, and irradiation at δ3.01 caused a simplification of the signals at δ2.85, 2.69 and 1.88. ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ207.0, 154.5, 152.4, 142.4, 139.2, 136.1, 131.2, 129.7, 128.83, 128.80, 128.0, 127.7, 127.2, 125.9, 124.6, 118.5, 116.0, 115.3, 107.7, 83.8, 65.0, 53.4, 46.8, 42.7, 41.1, 32.4; exact mass, m/z 458.1875 (calcd for $C_{32}H_{26}O_3$, m/z 458.1882), 278.0941 (calcd for $C_{18}H_{14}O_3$ ($M - C_{14}H_{12}$), m/z 278.0942).

b) A solution of ketone **181** (34.4 mg, 0.0561 mmol), AIBN (1.1 mg, 0.0067 mmol), and triphenyltin hydride (27.8 mg, 0.0792 mmol), in benzene (5.6 mL) was refluxed under argon for 15 h. The solvent was evaporated and flash

chromatography of the residue over silica gel (2 × 15 cm) with 8:1 hexane – ethyl acetate allowed separation of two diastereoisomers of **187**. The isomer with lower R_f (R_f = 0.36, TLC, silica, 5:1 hexane – ethyl acetate) was the major component (22.9 mg, 89%). The isomer with higher R_f (R_f = 0.42) was the minor product (1.5 mg, 5.8%). These compounds proved to be identical (TLC, ^1H NMR) with those described in the previous experiment.

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